



# ACTA MEDICA SCANDINAVICA

\*

## REDACTORES

GÖSTA BECKER Helsingfors	G. BERGMARK Upsala	H. I. BING Köbenhavn	R. EHRSTRÖM Helsingfors
F. FABER Köbenhavn	OLAV HANSSEN Oslo	ÖSTEN HOLSTI Helsingfors	SVEN INGVAR Lund
WILLIAM KERPPOLA Helsingfors	ANDERS KRISTENSON Stockholm	CARL MÜLLER Oslo	
EGGERT MÖLLER Köbenhavn	F. SALTZMAN Helsingfors	H. A. SALVESEN Oslo	
JON HJ. SIGURÖSSON Reykjavik	C. SONNE Köbenhavn	NANNA SVARTZ Stockholm	
ARVO VESA Helsingfors	ERIK WARBURG Köbenhavn		

J. G. G. BORST  
Amsterdam

W. A. KUENEN  
Leyden

C. D. DE LANGEN  
Utrecht

I. SNAPPER  
Amsterdam

EDITOR

I. HOLMGREN  
Stockholm



## COLLABORANT:

- IN DANIA: S. Bang, H. C. Gram, C. Holten, Aage Th. Jacobsen, E. Meulengracht, Aa. Nyfeldt, K. Schroeder, K. Secher.
- IN FENNIA: Erik Adlercreutz, Woldemar Backman, Bertel von Bonsdorff, Mons-Christlan Ehrström, Erik Hisinger-Jägerskiöld, Martin Savolin, Pauli Solsalo, J. Wahlborg, E. A. v. Willebrand.
- IN HOLLANDIA: F. S. P. van Buchem, J. Mulder.
- IN NORVEGIA: Olaf Bang, Gunnar Bøe, R. Hatlehol, Fr. Harblitz, H. F. Høst, Anton Jervell, G. H. Monrad-Krolin, K. Motzfeldt, Olaf Romeke.
- IN SUECIA: Erik Ask-Upmark, Hilding Berglund, Stig Björkman, Leonard Brahme, Arthur Engel, Birger Enocksson, Claes Grill, A. Gullbring, Sixten Hesser, Arnold Josefson, G. Kahlmeter, Kj. O. af Klercker, Eskil Kylin, Oscar Lindbom, Malte Ljungdahl, Haqvin Malmros, Gustav Nylin, Martin Odén, Ernst Sahlgren, Ernst B. Salén, Elsa Segerdahl, Birger Strandell, J. Tillgren, Jan Waldenström, Erik Wassén, A. Westergren, H. Öhnell.

HELSINGFORS 1945  
MERCATORS TRYCKERI

# INDEX.

Vol. CXX.

	Pag.
<i>Sven Akesson</i> (Stockholm): Pre-excitation and auricular fibrillation.....	1
<i>Håkon Rasmussen and Johs. Bce</i> (Oslo): The prognosis of essential hypertension, with remarks respecting the indications for operative treatment	12
<i>C. L. S. Bohn, E. Landboe-Christensen and C. M. Plum</i> (Copenhagen): On the importance of the duodenal glands of Brunner to the formation of red blood corpuscles in swine .....	32
<i>Sven Gard</i> ((Upsala, Sweden): Distribution of poliomyelitis virus in the intestines of normal mice .....	40
<i>Hans Heckscher</i> (Copenhagen): Cardiac and respiratory neurosis after contusions of the chest-wall .....	53
<i>Bertil Swedin and Åke Liljestrånd</i> (Stockholm): Spleen and liver abscesses due to Friedländer's bacillus .....	73
<i>Erik Jacobsen and C. M. Plum</i> (Copenhagen): The rôle of tyrosine in pernicious anemia .....	81
<i>Lennart Kirstein</i> (Stockholm): An after-examination of operated and non-operated cases with clinical symptoms of herniated discs .....	93
<i>Y. Edlund and Hj. Holmgren</i> (Stockholm): The rythmical variations of the liver glycogen and the pyruvic acid of the blood in experimental obstructive jaundice .....	107
<i>Asbjorn Hollermann and Helge Myhre</i> (Oslo): On gastritis .....	130
<i>V. Kafka</i> (Älvsjö-Stockholm): Über gerinnungsaktive Stoffe in der Cerebrospinalflüssigkeit .....	147
<i>Olov Lindahl and Bertil Josephson</i> (Stockholm): The kidney function and the renal clearances of some sulfanil-amide derivatives.....	195
<i>Gösta Ekehorn</i> (Stockholm): III. The normal excretion of urinary constituents of low tubular reabsorbability together with remarks concerning the variability of glomerular filtration .....	227
<i>Gösta Ekehorn</i> (Stockholm): IV. The clearance of various urinary constituents with special regard to certain particulars of their renal excretion ..	259
<i>U. S. v. Euler and T. Sjöstrand</i> (Stockholm): Pressor activity in urine in hypertension .....	276
<i>Thor Sällström</i> (Stockholm): The ulcer and wartlike.....	288
<i>Åge Kirkegaard and Gertrud Kirkegaard</i> (Slagelse, Denmark): Is there a primary, acquired hemolytic jaundice?.....	305
<i>Thor Sällström</i> (Stockholm): Regarding occupational factors in gastric ulcer and duodenal ulcer.....	340



	Pag.
<i>Hans Heckscher</i> (Stockholm and Copenhagen): The emphysema of the lungs, its symptoms and relations to other diseases.....	349
<i>Ole P. Nielsen and Erik Hertel</i> (Skive, Denmark): Leptospirosis Sejroe ....	384
<i>M. Ch. Ehrström</i> (Helsingfors): Hypoproteinämie- und Oedembereitschaft während des Krieges .....	399
<i>Henrik Lagerlöf</i> (Stockholm): Normal esterases and pancreatic lipase in the blood .....	407
<i>Jens Bang and O. Wanscher</i> (Copenhagen): The histopathology of the liver in infectious mononucleosis complicated by jaundice, investigated by aspiration biopsy .....	437
<i>H. O. Bang</i> (Copenhagen): Investigations on the use of the phycomyces method in the estimation of vitamin B in blood.....	447
<i>B. Chr. Christensen</i> (Copenhagen): Oscillometric studies .....	474
<i>B. Chr. Christensen</i> (Copenhagen): Studies on hyperventilation. ....	485
<i>Martti Hirvonen</i> (Helsingfors): Klinische Untersuchungen über die Polyzythämie. I ; .....	491
<i>G. Birath</i> (Stockholm): On the effect of oxygen-want and the conditions for its occurrence in chronic affections of the lung.....	527
<i>Johannes Zimmer</i> (Porsgrunn, Norway): Felty's syndrome: splenomegalia, leucopenia, and chronic polyarthritis. — Familial occurrence.....	543
<i>Martti Hirvonen</i> (Helsingfors): Klinische Untersuchungen über die Polyzythämie. II: .....	568
Volumes supplémentaires des <i>Acta Medica Scandinavica</i> publiés 1921—1945 .....	608
Revue des livres: .	
<i>F. Henschen</i> : V. Tronconi: I neurinomi dell'acustico.....	405

---

Supplementum CLIV, *Gösta Birath* (Stockholm): Lung volume and ventilation efficiency. Changes in collapse-treated and non-collapse-treated pulmonary tuberculosis and in pulmonectomy and lobectomy.

Supplementum CLV, *E. V. Helander* (Uleåborg, Finland): Über die Magensekretion bei Bothriocephalusträgern.

---

(From the Medical Clinic of Serafimerlasarettet, Stockholm. Head:  
Professor A. Kristenson.)

## Pre-excitation and auricular fibrillation.

By

SVEN ÅKESSON.

(Submitted for publication September 9, 1944).

In his recently ventilated treatise, entitled Pre-excitation a cardiac abnormality, Öhnell (1) gives the following explanation of the origin of the WPW electrocardiogram (earlier often referred to as the bundle of Kent): The pre-excitation complex is an electrocardiographic manifestation of two excitation waves acting simultaneously in the ventricles. Both waves are emitted by the auricular contraction. One travels down in the usual order through Tawara's node and the Bundle of His. The other, i.e. the extra excitation wave, sets in somewhat earlier than the ordinary one. It is either due to the mechanical stimulation of a hypersensible centre in the ventricle at auricular contraction, or to the fact that the impulse in the auricle is also directed down through a muscular connection between the auricle and the ventricle, thus arriving beforehand (since the ordinary impulse is physiologically retarded in Tawara's node). A hypersensible centre may, conceivably, be acquired owing to, for instance, myocarditis. The muscular connection, on the other hand, may be regarded as a congenital anomaly.

Schematically, the pre-excitation complex is composed of four parts:

I—from the beginning of the P wave to the beginning of the extra excitation.

II — from the end of I to the point where the slowly rising initial slope of the initial group of the ventricular complex abruptly bends upwards. As a rule, this coincides in all likelihood with the time at which the ordinary excitation wave starts to manifest itself.

III — from the end of II to the unknown point where both excitation waves meet.

IV — the rest of the ventricular complex.

As regards sections I—III, the electrocardiogram here constitutes a simple summation of the individual curves of the two exci-

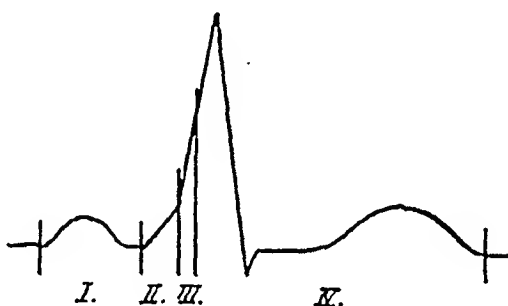


Fig. 1.

tation waves. As far as the remaining section is concerned, the appearance of each curve is by no means analysable, being deformed in an unknown way by the refractory regions of the other excitation wave.

The assumption of a simultaneous activity of two impulses at the registration of a pre-excitation complex is strongly borne out by the so-called concertina effect, described and introduced by Öhnell as a diagnostic aid. By means of different physiological and pharmacological procedures, the starting-time of either (or both) of the two excitation waves may be varied in relation to P. Thus, the QRS group may, for instance, be protracted by means of the retardation of the impulse, conducted down through the Bundle of His, owing to carotid sinus pressure, or it may be contracted owing to a shortening of the conduction time by means of atropine.

In the following, an account will be given of pre-excitation in a case suffering from hyperthyreosis. At the daily electrocardio-

graphic control, this case disclosed peculiar characteristics on a few occasions which are hardly explainable by Öhnell's two theories regarding the origin of the pre-excitation complex.

The case concerns a housekeeper of 42 years of age.

Her mother suffers from hypertonia and heart troubles. Otherwise, nothing of any interest regarding the heredity.

As a child, she had the measles and hooping-cough, possibly, also scarlet fever. She never had any polyarthritis.

In 1922, at the age of 20, tonsillectomy after repeated anginas. In 1939, she was operated on for uterus myoma.

In the summer of 1943, she noticed palpitation and shortness of breath while bicycling which had not troubled her before. In the autumn of the same year, she had a strange feeling, on and off, in the region of the heart and sensations of anguish simultaneously. In January 1944, influenza with a subfebrile temperature and cough. However, she did not go to bed. After about a month, an ache began to make itself felt in her ankles which also became somewhat swollen. No ache in her other joints. Furthermore, she sometimes noticed palpitation: a feeling of bubbling in her chest (the patient has had similar sensations, during her hospital stay, in connection with transient auricular fibrillation). A sensation of anguish again manifested itself simultaneously.

She called on a doctor who prescribed digitalis and quinidine, but she did not improve. She was remitted to Serafimerlasarettet on April 24th, 1944.

General condition slightly affected. Appears nervous and tired. Slight motorial agitation; does not lie still, fingers the cover.

Fairly thin and with weak musculature. Damp skin. Slight tremor of the fingers.

No Basedow symptoms from the eyes. The thyreoidea of normal size or but inconsiderably enlarged, of normal consistency.

The heart: A faint systolic murmur over the whole of the heart with punctum maximum over the apex. No palpable accent. Regular rhythm. A frequency of 108. Blood pressure 150/80. (A Röntgen picture of the heart revealed normal conditions).

Electrocardiogram: Regular rhythm. A frequency of 110. P-Q 0.10. QRS approximately 0.14. Ventricular complex of dextrogram type (the R wave in Lead II about 2 mv high), being biphasic in all the leads. The electrocardiogram of a typical WPW type (Fig. 2).

Normal blood values. Sedimentation rate: 25 mm/1 hour. The urine contained nothing pathological.

Attempts were made, during the subsequent days, to produce a concertina effect by means of carotid sinus pressure on the right and on the left side, atropine subcutaneously  $\frac{1}{2}$  and 1 mgm, and vasocordin  $\frac{1}{2}$  cm<sup>3</sup> intravenously. The carotid sinus pressure on the left side caused a distinct decrease in the frequency but, otherwise, gave rise to no definite

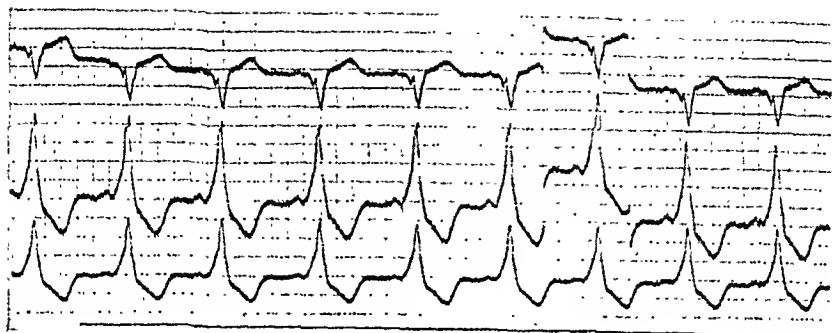


Fig. 2.

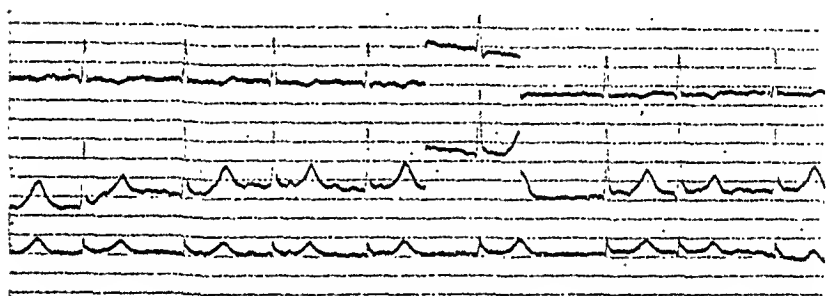


Fig. 3.

changes. After the vasocordin injection, an extrasystole without a compensatory pause was noticed, of the same appearance as other ventricular complexes. A clear concertina effect was unascertainable on all occasions.

The temperature was afebrile during the first weeks with a rise, on and off, of a few tenths. On account of the tendency towards loss of weight, in spite of rest and recumbency, hyperthyreosis was suspected. The relative metabolic rate was on May 5th + 91 per cent, being a few days later + 38 per cent and, afterwards, keeping at + 40 and + 50 per cent.

After attempts at internal treatment without any palpable effect, and owing to the appearance of transient auricular fibrillation, operation was decided upon. A pre-operative Lugol treatment was commenced on May 23rd.

The electrocardiogram remained the same the whole time, under practically daily control, (or revealed but insignificant changes which may, no doubt, be explained as due to a slight deviation in the position of the heart). The frequency was between 90 and 110. On May 10th a transient auricular fibrillation appeared which could not be ascertained at a control examination a few hours later. During the fibrillation, the ventricular complexes had an altogether normal appearance (Fig. 3): width of

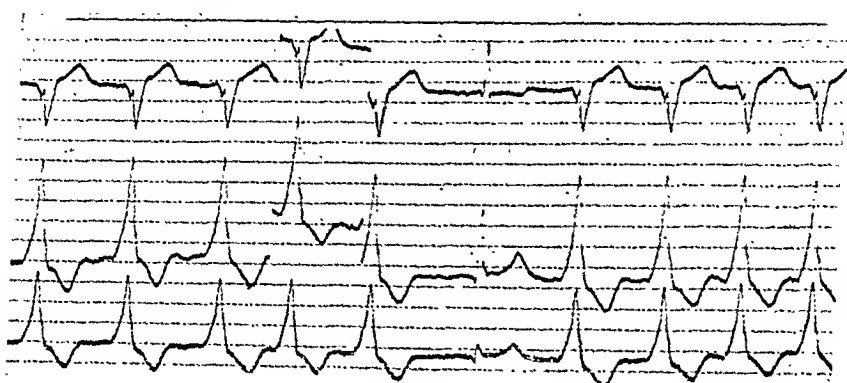


Fig. 4.

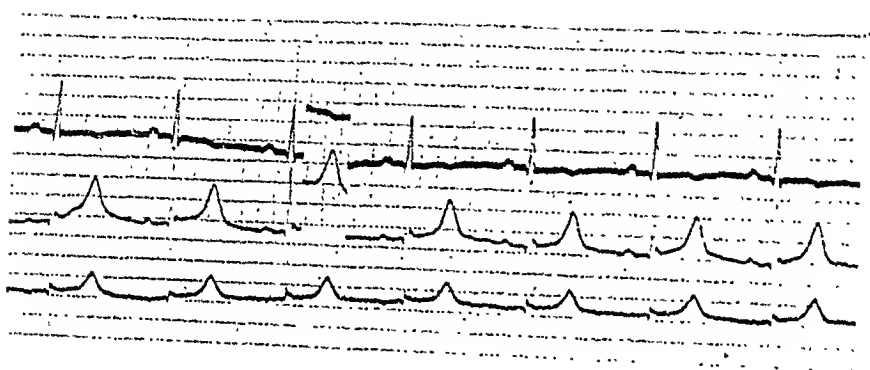


Fig. 5.

QRS being 0.07.  $T_I$  was, however, biphasic. The fibrillation waves were small. On May 19th, the patient was subjected to a new attack of fibrillation during which the pre-excitation type was maintained (Fig. 4). Only in one place was a ventricular complex noticed, of the same normal appearance as at the earlier attack of fibrillation, preceded by a P-like wave at a distance of 0.20 seconds. The fibrillation waves were very indistinct also this time.

After the introduction of the Lugol treatment, the condition of the patient rapidly improved. Her agitation disappeared. The pulse decreased to between 70 and 85. She slowly gained in weight. On June 7th, a regular rhythm was registered for the first time with regular ventricular complexes of the same normal appearance as during the first attack of fibrillation (Fig. 5).

The patient was subjected to operation on June 9th. Subtotal thyroidectomy was performed. The pathological-anatomical diagnosis of the preparation revealed a diffuse Basedow goiter. The WPW picture in the electrocardiogram reappeared in connection with the surgical intervention, remaining unchanged, in spite of the increasingly improved general con-

dition of the patient, at her discharge on June 27th. The relative met-

---

At a control examination, performed on July 28th, the electrocardiogram had again become normal.

Thus, a case of pre-excitation has been described above which revealed auricular fibrillation on two occasions. The first time, with normalization of the ventricular complexes, the second time, with maintained pre-excitation type of a constant appearance throughout the curve.

In what way may these findings be connected with the above-mentioned theories concerning the origin of the pre-excitation electrocardiogram? Before entering upon this question, a brief account will be given regarding the various conceptions of the genesis of auricular fibrillation.

Three theories will, principally, be met with in the literature (2, 3) on this subject. The first theory was propounded by Engelmann who declared that fibrillation constitutes a manifestation of masses of extrasystoles from different parts of the auricles. At first, his opinion was shared by Winterberg, as well as Lewis, and was further elaborated by them. However, later on, at experimental investigations, Winterberg and Rothberger made the observation that mechanical as well as electrical oscillations at fibrillation may, for long periods, appear rhythmic and coordinated within different parts of the auricles, speaking in favour of a uniform origin of the excitation impulses. They believed that fibrillation was due to the fact that a centre in the auricle suddenly starts emitting impulses of a very high frequency (3000—3500/min.) in the adjacent musculature (i.e. tachysystolia). The rapid frequency in itself would involve an irregular response from Tawara's node. The frequency is lower at auricular flutter. However, there is no principle difference as between fibrillation and flutter.

In contrast, Garrey (2) states that such a strong abbreviation of the refractory period in the auricular musculature is hardly conceivable, being a prerequisite with regard to this theory. Moreover, he was able to prove that the excitation wave in a muscular bridge, partially cut loose from the auricle but with maintained contact at both ends, ran now in one direction now in the other. This could not be considered as compatible with the conception of only one

focus of the impulses. Thus, basing his opinion on his own observations and Mines' classic experiment<sup>1</sup>, Garrey laid down the hypothesis of the dependency of flutter and fibrillation on a so-called circulus movement. An excitation wave would, in the case of flutter, circulate in the auricle in one direction and, on its return to the starting-point, constantly find new excitable tissue, either on account of a shortened refractory period, or reduced conduction rapidity. It would, accordingly, give rise to the next excitation movement by itself.

At fibrillation, the high frequency causes the excitation wave to encounter in its course fibres which are in a refractory period. This impels the wave to find new paths, thus giving rise to constantly new circulation movements. This theory, which has been subjected to further analysis in a series of works by Lewis, is undoubtedly nowadays the one generally accepted, although criticism has not been lacking. Rothberger (4) points out that the difference is small between this theory and the conception of a tachysystolic focus when, in conformity with Lewis (5) the diameter of the circulation course may, at fibrillation, be assumed to equal not more than a few millimetres.

As far as details are concerned, opinions still differ.

Thus, Lewis believes that the excitation wave constantly travels, on the whole, in the same path (the mother wave) and emits impulses during its course, on and off, into the neighbouring musculature. Inter alia, the objection has been raised (by Rothberger) that no preformed muscular track, corresponding to the condition in Mines' experiment, exists in reality and, further, that if Lewis' statement were correct, one of the auricles must cease to fibrillate when the boundary between them is severed. This was, in fact, proved not to be the case by Brans and Katz (3). They declare that, in the case of fibrillation, masses of daughter waves must be involved (a viewpoint already held earlier by Garrey), or multiple foci.

---

<sup>1</sup> A muscle ring consisting of the ventricular wall of a tortoise heart, the apex and base of which had been cut away, was compressed in one place with a clamp. The muscle was then stimulated near the clamp by means of an induction shock so as to cause an excitation wave to set off in a direction away from the blocking clamp which was afterwards immediately removed. When the excitation wave returned to the starting-point, the refractory period had ended, thus permitting the wave to pass on after each round.



Scherf (6), as late as in 1940, was sceptical towards the theory of a circus movement. In his own experiments (7), a blocking of the track of the excitation wave, as supposed by Lewis, failed to check the flutter or change its appearance. Cases of flutter, described earlier, in which the auricular frequency suddenly decreased to half may also be more easily explained by the assumption of a tachysystolic centre which is suddenly 2:1 blocked. Moreover, it would be strange if fibrillation, when caused by multiple excitation waves, could suddenly disappear and give way to normal beats.

Whether or not a circus movement does occur at fibrillation, or a single focus, or several foci emitting frequent impulses, it is, nevertheless, apparent that the excitation course at fibrillation of a high frequency must, at least, become extremely irregular. The impulse waves, which, under normal conditions, spread out as rings on the surface of the water, continually encounter blocked muscle fibres in a refractory period and, consequently, have to find new tracks. Even if the original impulse is emitted from a uniform centre, possibilities exist of the appearance of innumerable secondary circular impulses, which are of different sizes and invariably changing.

In what way should, then, the pre-excitation complex change at fibrillation, if its origin is contingent to a muscular connection between auricle and ventricle? It is, apparently, exceedingly improbable that active impulses from the auricle will reach Tawara's node and the starting-point of the muscle bridge at the same time interval as under normal conditions, or, at fibrillation, from one beat to the other. Even if this is quite conceivable, it is, nevertheless, difficult to assume that the intermittent blocking between the auricle and the ventricle would occur identically in the specific and the unspecific musculature. According to Lewis (8), the refractory period in the specific tissue is longer by 30 per cent. The consequence would be a constantly varying time interval between the start of the two excitation waves; the concertina effect would appear to a varying degree from one beat to another. This did not happen here; the different ventricular complexes were almost completely identical throughout the curve. Thus, the explanation of a muscular connection between auricle and ventricle must, in this instance, be strongly rejected. Feldmann and Koch (9) arrive at the same conclusion in a case described by them.

What should, then, be expected to happen when the fibrillation sets in, if the extra impulse is emitted by mechanical stimulation when the auricle is contracted. At fibrillation, the mechanical effect of the incoordinated, faint and limited fibrillar contractions of a high frequency in the auricle will be completely or almost completely non-existent. Thus, the extra impulse should disappear and with it the pre-excitation type of the ventricular complex, as happened at the first attack of fibrillation. However, at the second attack, the abnormal complexes remained unchanged, as described above.

Even if it were possible to assume that a mechanical stimulation from the auricles would be able to manifest itself intermittently, this would have to happen at times completely uncorrelated to the conducted impulse; also in this case, the concertina phenomenon would appear. Thus, not even the explanation of a hypersensible centre in the auricle can be the correct one.

The genesis of the pre-excitation complex is, evidently, still doubtful in certain cases.

It may be possible, with regard to the present case, that a muscular connection exists between the auricle and the ventricle but that the conducted impulse rapidly passes over to the Bundle of His or a main branch and, in this way, causes the blocking of all conduction through Tawara's node; the pre-excitation complex is only built up of one excitation wave. Seherf, who has interpreted the genesis of the pre-excitation complex similarly, also gives a description, together with Schönbrunner (10), of a case of fibrillation with WPW, without evincing any surprise. The initial slope of QRS is, in fact, sufficiently steep to keep well within the order of magnitude at bundle branch block. The faint slope is lacking which would speak in favour of a more peripheral start in the ventricle. Nor was it possible to provoke any definite concertina effect. However, it is hard to explain why, on one occasion, all conduction took place through the muscular connection, while, on the other, exclusively in the normal way through the Bundle of His.

Another hypothesis, which is quite conceivable in this connection, is the one propounded by Lepeschkin (11), proceeding from Pezzi's (12) theory of a division of Tawara's node and observations by, *inter alia*, Condorelli (13) and Pines (14). Pezzi uses the

following picture: The excitation wave from the sinus node arrives by train at the Tawara station where the train stops and impulses are loaded over on to two trains, each for one of the main branches. It is quite conceivable that one of the trains starts earlier or runs faster than the other. This would explain the short P-Q time and the transformation of the ventricular complex in the direction of a type of bundle branch block. According to the opinion of the present author, the point where one of the branches within Tawara's node issues might, possibly, be blocked from the vagus so that the impulse would pass through it freely and rapidly. (As late as in 1941, in his interpretation of the so-called reciprocating beats, Scherf (15) assumed a functional longitudinal cleaving of Tawara's node. Furthermore, he mentions in this connection that Cooke and White state, in a personal communication, that the WPW syndrome was explainable by the assumption of a longitudinal dissociation in the auriculoventricular conduction system with faster conduction in one bundle branch). A vagal excitation by, for instance, carotid sinus pressure would not prolong the distance between P and the pre-excitation complex, which is determined by the blocked branch, but would, certainly, not be hindered from affecting the other branch and, in that way, even give rise to a concertina effect. At fibrillation, each impulse, which was at all able to penetrate into Tawara's node, would send off two trains at short intervals in the usual order. At the normalization, the blocking of the vagus would disappear. The hypothesis does not hold good with regard to instances of a faint initial slope of QRS (or must be supported by further hypotheses, as pointed out by Lepeschkin (11).)

Finally, yet another possibility will be mentioned. Perhaps, fibrillation in the usual sense does not occur, but rather paroxysmal tachycardia which has occurred owing to a circulus movement, as described by de Boer (16), which at the first attack of fibrillation passes down through the Bundle of His and up through the muscular auriculoventricular connection, and in the opposite direction at the second attack. However, also in this case the impulse conducted down through the muscular connection must be assumed to execute the building up of the pre-excitation complex on its own.

Thus, it appears as though at least one other possibility has to

be added to Öhnnell's two theories regarding the genesis of the pre-excitation complex. In the case described in this paper, the theory supported by Lepeschkin, regarding the faster conduction of the impulse in one of the main branches, seems to be the most appropriate one with regard to the above-mentioned facts.

### Summary.

A description is given of a case of hyperthyreosis with an electrocardiogram of the pre-excitation type. At one attack of fibrillation, a simultaneous normalization of the ventricular complexes occurred, at another, the abnormal ventricular complexes remained unchanged. Auricular fibrillation with pre-excitation is hardly explainable, either by an extra impulse through an unspecific muscular connection between auricle and ventricle, or by a hypersensible centre in the ventricle which is stimulated mechanically at auricular contraction. A faster conduction of the impulse in one of the main branches of the Bundle of His constitutes a possible explanation.

### Literature.

1. Öhnnell, R.: Pre-excitation, a cardiac abnormality. *Acta med. scand.* (1944). — 2. Garrey: *Physiol. Rev.* 4. 215 (1924). — 3. Brams and Katz: *Amer. Heart Journ.* 7. 249 (1931—32). — 4. Rothberger: *Klin. Wochschr.* 1922: 1, 82. — 5. Lewis, Dry and Iliescu: *Heart* 8. 311 (1921). — 6. Scherf and Boyd: *Clin. electrocardiography*. St. Louis 1940. — 7. Scherf: *Zeitschr. f. d. gesamt. experim. Med.* 61. 30 (1938). — 8. Lewis, Drury and Iliescu: *Heart* 9. 21 (1921—22). — 9. Feldmann und Koch: *Zeitschr. f. Kreislafforsch.* 35. 512 (1943). — 10. Scherf und Schönbrunner: *Zeitschr. f. klin. Med.* 128. 750 (1935). — 11. Lepeschkin: *Das Elektrokardiogramm*. Dresden und Leipzig 1942. — 12. Pezzi: *Arch. Malad. du coeur* 25. 249 (1932). — 13. Condorelli: *Verh. deutsch. Gesellsch. f. Kreislaff.* 5. 292 Dresden 1932. — 14. Pines: *Wien. Arch. f. klin. Med.* 32. 129 (1938). — 15. Scherf: *Arch. of intern. med.* 67. 371 (1941). — 16. de Boer: *Arch. Malad. du Coeur* 20. 281 (1927).
-

From Medical Department B, Rikshospital, Oslo. (Chief: Professor  
H. A. Salvesen, M. D.)

## The Prognosis of essential Hypertension, with remarks respecting the indications for operative treatment.

By

HÅKON RASMUSSEN and JOHS. BØE.

(Submitted for publication October 2, 1944).

---

In 1938 H. Rasmussen and R. Thingstad studied the cardiovascular changes in 100 cases of essential hypertension (*Acta Med. Scand.* 1939: 101: 237). In 1943 this material was re-investigated, with the results which will here be recorded.

The questions we especially proposed to consider were the following: Is it possible from the cardiovascular and renal phenomena noted in the material investigated in 1936—1938 to draw prognostic conclusions, 1) with respect to the danger of death, 2) as regards the manner of death, whether it may be due to cardiac insufficiency, cardiac infarction, an apoplexy or renal insufficiency. The answering of these questions has become still more important through introduction of operative treatment of essential hypertension, aiming either at relief of symptoms or lengthening of life or both. In order to form a judgment regarding the results of an operation it is requisite to have an exact knowledge of the prognosis in case of conservative treatment.

Among the survivors it was of especial interest to follow the subsequent development of the illness, noting any alterations in blood pressure and to what extent further damage was sustained by

Table 1.  
Survey of the material on re-examination.  
Causes of death.

Dead .....	52	
Alive .....	44, whereof re-examined 39.	
Not found .....	4	
Total		100
Causes of death.		
Known causes	50	
Unknown causes	2	
Cardiac insufficiency .....	11	In all 22 died of heart disease—44 % of known causes of death.
Myocardial infarction .....	9	
Pneumonia + cardiac insufficiency	2	
Cerebral hemorrhage .....	19—38 %	
Uremia .....	3—6 %	
Other causes of death:		
Pneumonia .....	3	Total 12 %
Prostatic operation .....	1	
Cerebral arteriosclerosis (psychosis)	1	
Cholecystitis .....	1	
Total		50 known causes of death.

the different organs, the heart with the coronary arteries, the cerebral vessels and the kidneys.

Details respecting the cardiovascular and renal status of the 100 patients investigated will be found in the previous publication. The material consists mainly of elder hypertension patients in a rather advanced stage of the disease, as is usual in hospital cases, many of them having an already far advanced hypertensive heart disease. The blood pressure here recorded is not the high pressure noted on admission to hospital, but the pressure found after the patient had been lying in bed for 8—14 days, usually with a diet poor in proteins. All were cases of fixed hypertension.

The average period of observation was six years, twenty-six patients having been examined in 1936, fifty-one in 1937 and twenty-three in 1938. In Table 1 is given a survey of the results of the re-examination. 52 of the patients have died, 44 are alive and 39 of these have been reexamined, while 4 could not be traced. In 2 cases the causes of death are unknown, while in the remaining 50

Table 2.

Age distribution in the whole material and in the living group and the deaths.

Age	30—34	35—39	40—44	45—49	50—54	55—59	60—64	65—69	70—74	75—79	80—84	Women	Men
Total material .....	1	2	1	6	15	19	27	14	9	4	2	69	31
Alive .....		1		5	6	11	13	6	2			36	8
Dead .....	1	1	1	1	9	7	12	7	7	4	2	30	22
Deaths from heart failure					2	3	2	3	1	1	1	7	6
Death from myocardial infarction .....					1	1	3	2	1	1		7	2
Deaths from cerebral hemorrhage .....	1			1	4	3	5	2	3			11	8

they are as follows: 13 patients died of cardiac insufficiency, that is to say, 13 per cent of the whole material, or 26 per cent of the number of deaths, 9 died of myocardial infarction, making 18 per cent of the deaths. Thus 44 per cent altogether died of heart affections. 19 patients, or 38 per cent, died of apoplexy, and 3 patients (6 per cent) died of uremia. Our knowledge of the causes of death is to a large extent based upon the reports and diagnoses of other doctors, and there may be some doubt as to at least one, perhaps two of the cases where the death was ascribed to uremia. Six per cent is therefore to be taken as a maximum figure.

Table 2 shows the distribution according to sex and age (age in 1936—1938) for the whole material and for the living and dead patients: Of the 69 women there are more survivals than deaths, whereas among the 31 men there are three times more dead than living. The well-known fact that hypertension is more dangerous for men than for women is thus clearly revealed by the figures. The mortality is fairly evenly distributed among the different age-groups. Cardiac insufficiency and myocardial infarction are found to be more strongly represented in the higher agegroups, whereas apoplexy is more frequent in the lower ages.

Table 3 gives an idea of the serious character of the hypertension in this material, seeing that 34 patients, or 34 per cent, died in the course of 2 years.

Table 3.

Time elapsed from hospital observation 1936—38 to death.

Died in 1st year	21
Died in 2nd year	13
Died in 3rd year	9
Died in 4th year	5
Died in 5th year	3
Died in 6th year	1
Total	52

The importance of the systolic pressure for the prognosis appears from *Table 4*. The mortality increases with rising blood pressure. In the three blood pressure groups the frequency of apoplexy rises from 23 to 39 and to 43 per cent, while the deaths from cardiac causes do not show a similar increase, but are on the contrary more frequent at low pressure. Also the diastolic pressure, *Table 5*, shows an increasing mortality with rising pressure, so that in the third group, with diastolic pressure equal to or above 125 mm Hg, three-fourths of the patients died. Here we find the same situation as in case of systolic pressure: increasing mortality with rising pressure, half of the patients in the third group having died of apoplexy, while the mortality from heart affections does not increase with the diastolic pressure, but is highest in the groups with lower pressure. On subtracting the deaths from apoplexy, cf. *Tables 4 and 5*, we find that the mortality from causes other than apoplexy is but little affected by the rise in blood pressure, either systolic or diastolic. The conclusion to be drawn herefrom is that when the mortality increases with rising height of blood pressure, systolic or diastolic, this is due to the increasing frequency of apoplexy.

The importance of the size of the heart for the prognosis is seen from *Table 6*. The mortality rises considerably with increased size of heart and the greater mortality is mainly due to cardiac causes. This applies especially to cardiac insufficiency, which in patients with the largest hearts is the cause of half the deaths, but myocardial infarctions likewise show increased frequency according as the size of the heart increases. Three-fourths of the deaths among patients with the largest hearts were due to heart disease.



Table 4.

Height of the systolic Blood Pressure in Relation to Mortality and Causes of death.

Systolic blood pressure	Total	Alive	Died	Deaths from cerebral hemorrhage subtracted from total deaths	
160—179 mm Hg Group I	32	19 59%	13 41%	10 31%	Cardiac insufficiency 4=31% Myocardial infarction 4=31% Cerebral hemorrhage 3=23% Uremia 1 Other causes 1
180—199 mm Hg Group II	33	15 45%	18 55%	11 33%	Cardiac insufficiency 3=17% Myocardial infarction 2=11% Cerebral hemorrhage 7=39% Uremia 1 Other causes 3, unknown 2
≥ 200 mm Hg Group III	31	10 32%	21 68%	12 39%	Cardiac insufficiency 6=28% Myocardial infarction 3=14% Cerebral hemorrhage 9=43% Uremia 1 Other causes 2

Table 5.

Height of the diastolic Blood Pressure in Relation to Mortality and Causes of death.

Diastolic blood pressure	Total	Alive	Died	Deaths from cerebral hemorrhage subtracted from total deaths	
90—109 mm Hg Group I	46	26 57%	20 43%	16 35%	Cardiac insufficiency 7=35% Myocardial infarction 5=25% Cerebral hemorrhage 4=20% Uremia 1 Other causes 3
110—124 mm Hg Group II	31	13 42%	18 58%	10 32%	Cardiac insufficiency 3=17% Myocardial infarction 1=6% Cerebral hemorrhage 8=44% Uremia 2 Other causes 2, unknown 2.
≥ 125 mm Hg Group III	19	5 26%	14 74%	7 37%	Cardiac insufficiency 3=21% Myocardial infarction 3=21% Cerebral hemorrhage 7=50% Uremia 0 Other causes 1

The prognostic importance of the electrocardiogram is seen from Table 7. The type-classification of left ventricular enlargement curves is given in the previous work, as well as in Fig. 1. The expression »hypertrophy electrocardiogram» is used, although dilatation is perhaps the most important feature. With increasing degree of left ventricular hypertrophy (higher electrocardiographic type-number) the rate of mortality is seen to increase. Of the patients with well developed left ventricular hypertrophy (Type III) three-fourths died and of the 7 with left bundle branch block 100 per cent, four of them already within one year. In the six surviving patients with Type III this type of electrocardiogram was observed during from 7 to 9 years. Deaths from cardiac insufficiency increase with increasing degree of left ventricular hypertrophy in the electrocardiogram. The myocardial infarctions, on the other hand, and likewise the apoplexies show no relation to the type

Table 6.

Heart Size, radiologically determined in Relation to Mortality and Causes of death.

Heart size	Total Material (95)	Alive	Died	Causes of death
Normal or slightly enlarged Cardio-thoracic index $\geq 1.90$	34	23 68%	11 32%	Cardiac insufficiency 0=0 % of all { Cardiac death 9 % Myocardial infarction 1=9 % deaths Cerebral hemorrhage 5=45% Uremia 1 Other causes 4, whereof 1 unknown
Moderate cardiac enlargement Cardio-thoracic index $-1.70-1.89$	37	16 43%	21 57%	Cardiac insufficiency 3=14% of all { Cardiac death 28 % Myocardial infarction 3=14% deaths Cerebral hemorrhage 11=52% Uremia 2 Other causes 2
Grossly enlarged hearts. Cardio-thoracic index $\geq 1.69$	25	5 20%	20 80%	Cardiac insufficiency 10=50% of all { Cardiac death 75 % Myocardial infarction 5=25% deaths Cerebral hemorrhage 3=15% Uremia 0 Other causes 2, where of 1 unknown

Table 7.

Electrocardiographic Changes in Relation to Mortality and Causes of Death.

Electro-cardiographic type	Number total 95	Alive	Died	Causes of death	
Normal	31	23 74%	8 26%	Cardiac insufficiency 0—0% Myocardial infarction 2— Cerebral hemorrhage 4—50% Uremia 1 Other causes 1	25% cardiac death
Left ventricular hypertrophy Type I	3	0	3	Cardiac insufficiency 1 Myocardial infarction 1 Cerebral hemorrhage Uremia Unknown cause 1	
Left ventricular hypertrophy Type II	14	7 50%	7 50%	Cardiac insufficiency 1—14% Myocardial infarction 2 Cerebral hemorrhage 2—30% Uremia 1 Other causes 1	43% cardiac death
Left ventricular hypertrophy Type III	22	6 27%	16 73%	Cardiac insufficiency 6—37% Myocardial infarction 2 Cerebral hemorrhage 6—37% Uremia 0 Other causes 2	In 6, still alive, electrocardiogram is observed: In 4 for 7 years In 1 for 8 years In 1 for 9 years
Left ventricular hypertrophy. Type IV. Left b. branch block	7	0	7 100%	Cardiac insufficiency 3—43% Myocardial infarction 0 Cerebral hemorrhage 4—57% Uremia 0 Other causes 0	43% cardiac death 4 died within 1 year. 2 died within 2 years 1 died within 3 years.
Atypical electrocardiograms	19	8 42%	11 58%	Cardiac insufficiency 2 Myocardial infarction 2 Cerebral hemorrhage 3 Uremia 1 Other causes 3, where- of 1 unknown	3 Wilson-block-whereof 1 still alive, 2 died, 1 of cerebral hemorrhage, 1 of pneumonia

Table 8.  
Proteinuria in Relation to Mortality and Causes of death.

Proteinuria	Total	Alive	Died	Causes of death
None	51	28 55%	23 45%	Cardiac insufficiency 3 Myocardial infarction 5 Cerebral hemorrhage 8 Uremia 2 Other causes 5, unknown 2
Inconstant	21	12 57%	9 43%	Cardiac insufficiency 2 Myocardial infarction 2 Cerebral hemorrhage 4 Uremia 1 Other causes 0
Constant	24	4 17%	20 83%	Cardiac insufficiency 8 Myocardial infarction 1 Cerebral hemorrhage 8 Uremia 0 Other causes 3 (pneumonias)

of electrocardiogram. It is here to be noted that in case of normal electrocardiogram the mortality from myocardial infarction is equally great as, or greater than in the group with left ventricular hypertrophy. This supports the previously advanced view (6 and 7) that the electrocardiogram of left ventricular hypertrophy is not due to changes in the coronary arteries.

Of 16 patients who are registered as suffering from angina pectoris 10 have died. 4 of them from cardiac insufficiency, 3 from myocardial infarction, 2 from apoplexy and 1 from pneumonia, while 6 are still alive three of them being now free from angina pectoris. Three of the nine patients who died of myocardial infarction had angina pectoris in 1936—1938. Two patients had, or had had, myocardial infarction in 1936—1938. Both of them have died, one of a new infarction, the other of cardiac insufficiency.

Table 8 gives a survey of the relation of proteinuria to the prognosis. The group without proteinuria and the group with transient proteinuria behave alike, the mortality being about the same as for the whole material. The group with constant, but never extreme

Table 9.

Renal Function (Urea Clearance) in Relation to Mortality and Causes of death.

Urea-clearance	Total	Alive	Died	Causes of death
$\geq 50$ %	50	27 54%	23 40%	Cardiac insufficiency 4 Myocardial infarction 3 Cerebral hemorrhage 11 Uremia 1 Other causes 2, thereto 2 unknown
26—49 %	26	12 46%	14 54%	Cardiac insufficiency 2 Myocardial infarction 1 Cerebral hemorrhage 7 Uremia 2 Other causes 2
$\leq 25$ %	2	1	1	Myocardial infarction 1

proteinuria shows a considerable increased mortality rate, more than 80 per cent having died, some from cardiac insufficiency, some from apoplexy, equally many from each cause. In case of death from cardiac insufficiency it is no doubt a question of stasis proteinuria, while the great frequency of apoplexy in case of constant proteinuria is more difficult to explain. None of the three deaths from uremia occurred in the group with constant proteinuria. Two of the four survivors with constant proteinuria have proved to have pyelonephritis with renal calculi.

The renal function, judged by the urea clearance (the concentration test was also applied), and its relation to the prognosis will be seen from Table 9. Whether the renal function is normal or more or less reduced, we find essentially the same relation between living and dead patients. The three deaths from uremia are distributed between one patient with normal and two with slightly reduced renal function.

The ophthalmoscopic findings in the material are somewhat difficult to appraise, partly owing to summary descriptions. None of the patients have had severe affections of the retina, with hemorrhages and degenerative foci. Of the 17 patients described as having

more or less severe papillary edema twelve died and five are alive. Two died of cardiac insufficiency, six of apoplexy and two of uremia. These latter may be regarded as cases of malignant hypertension. Retinal arteriosclerosis was recorded in 16 cases. Of these patients 14 are dead, one from cardiac insufficiency, one from myocardial infarction, 8 from apoplexy and one from uremia.

Of 7 patients with diabetes mellitus 2 have died, while 5 are alive.

Thus we find that deaths from cardiac insufficiency in case of essential hypertension have no special relation to the height of the blood pressure, but rather seem to be most frequent among patients with low pressures, which doubtless indicates that heart failure has already exerted an influence. The deaths from cardiac insufficiency likewise seem to have no relation to the renal function, but they distinctly increase in number with increasing size of the heart and with increasing degree of left ventricular hypertrophy in the electrocardiogram. The constant (stasis) proteinuria is also frequent. The significance of the size of the heart and the great prognostic importance of the electrocardiogram are shown by the fact that 10 of the 13 deaths from cardiac insufficiency occurred in the group of patients with enlarged hearts and 9 of the 13 in the group with left ventricular hypertrophy electrocardiogram of Type III and Type IV.

The deaths from myocardial infarction among patients with essential hypertension are not distinguished by any characteristic features as regards blood pressure, size of heart, proteinuria or renal function. Only one-third of the nine who died had angina pectoris in 1936—1938 and, conversely, only three of the sixteen with angina pectoris died of myocardial infarction. The prognosis in case of myocardial infarction here seems therefore difficult to establish.

Death from apoplexy in cases of essential hypertension shows, first and foremost, a distinct relation to the height of the blood pressure, especially the diastolic pressure, while changes in the eye-ground, papillary edema and retinal arteriosclerosis are also frequent. Nine of the nineteen patients who died of apoplexy had a blood pressure equal to or higher than 200 mm Hg, and 15 of the 19 had a diastolic blood pressure of 110 mm Hg, or higher. From this it is clear that the height of the blood pressure is of great prognos-

the significance as regards the mortality from apoplexy, but it must again be mentioned that we are here not dealing with blood pressures on admission to hospital or ambulant pressures, but with the pressures after 8—14 days' rest with light dieting.

The deaths from uremia in this material are characterized at most by changes in the eye-ground, by papillary edema and arteriosclerosis, but otherwise show no relation to height of blood pressure, size of heart, electrocardiogram, proteinuria or impairment of the renal function at the time of observation. Thus the deaths from uremia, like those from myocardial infarction, seem difficult to prognosticate.

### Clinical findings in the surviving patients re-examined.

Of the 44 survivors, 36 women and 8 men, 39, including 7 men, have been re-examined, 34 of them being kept under observation in hospital. The known duration of the disease in the different patients was as follows: 5 years in 4 patients, 6 years in 10, 7 years in 11, 8 years in 4, 9 years in 4, 10 years in 1, 11 years in 2, 14 years in 1, 15 years in 1, and 18 years in 1.

The general impression given by this group is that it consists of patients who have either been able to, or been inclined or obliged to spare themselves as much as possible. Four of them are greatly and seven more moderately incapacitated by their disease. Of two patients who previously had considerable cardiac insufficiency one has improved. Of 19 with less severe insufficiency, in the form of dyspnea on exertion, ten have got better, while one has become worse. Two of the patients have had myocardial infarction and five have developed angina pectoris, while in three cases angina pectoris has disappeared. Four patients had had apoplexy already before the first time of observation. Two are considerably invalided thereby and one has since had several attacks. Thirteen patients are troubled, some of them greatly, by chronic hypertensive encephalopathy, with headache, vertigo, buzzing in ears, throbbing in the head etc.

One patient with the supplementary diagnosis of lues latens (B. P.: 230/120) had got syphilitic aortitis with aortic insufficiency (B. P. 210/100). On re-examination cancer of the stomach was found in one patient, who died after operation. Two patients were

found to have renal calculi and pyelitis. These were then no longer regarded as patients with essential hypertension, but as cases of pyelonephritis with hypertension.

Alterations in blood pressure from the previous observation till 1943 were, like all numerical fixation of blood pressure, difficult to establish. In 5 patients the blood pressure is deemed to have risen, in 23 to be unaltered, while in 11 it is considered to have fallen (Table 10). Three of these eleven have got distinctly lower, but still elevated pressures.

*Example:* Patient No. 77, b. 1890. Woman. Hypertension since pregnancy in 1929. When in hospital in 1932, 1935 and 1936 she had fixed hypertension, in spite of staying in bed and keeping diet, with blood pressure about 240/150 and 220/135. In 1944 the pressures during 8 days' observation were 250/160. 170/110 and 160/110.

In 6 of the 11 patients with fall in pressure the hypertension has passed over from a fixed to a labile stage.

*Example:* Patient No. 12, b. 1878. Woman. During protracted stay in hospital in 1934 and 1936 she had fixed hypertension, about 245/150 and 190/120. In 1943 the pressures are 240/130, 130/90 and 135/70.

In two patients the blood pressure has become normal.

*Example:* Patient No. 18, b. 1871. Woman. In 1937 B. P.: 175/100, and 165/110. In 1941 ambulant B.P. 145/80.

Cardiac insufficiency as cause of the fall in blood pressure was not present in any of these patients. Of the 7 men 6 have unaltered blood pressure, while in one case the pressure is normal.

The re-investigation of the size of heart has unfortunately not been very successful, as the cardio-thoracic index proved to be quite worthless as basis for comparison between the findings in 1936—1938 and the findings in 1943. This is due to an obvious difference in the roentgenological technique, the pictures in the last examination being taken at a point approaching maximum inspiration and in the earlier investigation at a point nearer to maximum expiration. A contributory cause of the divergency lies in the fact that 12 of the 39 patients (possibly owing to the food situation due to the war) have lost over 10 kg in weight, one of them as much as 30 kg. For these reasons the height of the diaphragm and the breadth of the thorax now show great differences from the figures



Table 10.  
Changes in clinical Status, six years after first Examination.

	Deterioration	No change	Amelioration	Normal findings after 6 years' observation
Blood pressure	5	23	11	2
Heart size	6 undoubtful 4 slighter and doubtful	14	2 doubtful	23
Electrocardiogram	14	22	3	18
Renal function	2 undoubtful 6 doubtful	24	3 doubtful	26

found in 1936—1938. A rough and ready estimation, which is also sometimes difficult, had therefore to be employed, and for this purpose we had at disposal films for only 26 patients from the previous investigation. In 6 of these the heart now shows an undoubted increase in size, in 4 a doubtful increase, while in 14 cases it is unaltered and in 2 cases has possibly become smaller. An important point is that in no less than 23 of these 39 patients after such long-continued hypertension the size of the heart still remains within the normal limits.

The electrocardiographic abnormalities (Table 10) have increased in 14 cases, in 22 cases there is no change and in 3 there is improvement. Among the 22 unaltered patients there are 15 with normal electrocardiogram and 2 with deep QIII as the only pathological finding. Among the 14 patients showing deterioration during the period of observation 2 have now infarction curves in addition to earlier hypertrophy curves. Ten patients have got newly-developed hypertrophy curves. Seven of these have now, instead of the original normal electrocardiogram, developed hypertrophy curves of Types II and III (Figs. 1 and 2), while three have passed over from Type II to Type III. One patient has now passed from

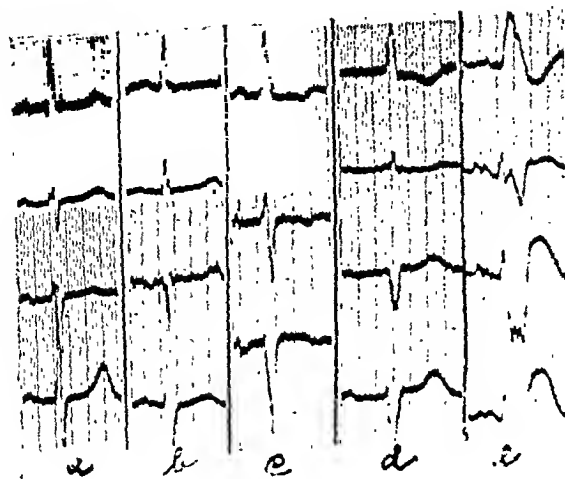


Fig. 1.

The four electrocardiographic types, characteristic of left ventricular enlargement (dilatation and hypertrophy).

- a. normal electrocardiogram with left axis deviation.
- b. Left ventricular enlargement, type I
- c. " " " type II
- d. " " " type III
- e. " " " type IV. Left bundle branch block.

a normal to a non-characteristic pathological electrocardiogram. Three patients show a regression of the pathological changes. One of them who had left ventricular hypertrophy of Type III has now a normal electrocardiogram, one with Type III has now got Type II, while one who had Type I has now a normal curve. Thus after these six years of observation 17 patients out of 29 have still a normal electrocardiogram.

These observations tend to confirm the previously suggested classification of types of left ventricular hypertrophy curves. It would have been of interest to compare the alterations in size of heart with the electrocardiographic changes, but such comparison cannot here be made with certainty. Certain it is, however, that three of the six patients with considerable increase of heart size during observation have at the same time from a normal electrocardiogram developed Type II (two patients) or Type III (one patient). Three others, on the contrary, with development of electrocardiogram of left ventricular hypertrophy showed no certain enlargement of the heart. It is interesting to note that one patient in whom the size of the heart was considerably increased, while



Fig. 2.

Examples of electrocardiograms showing deterioration or amelioration of pathological condition.

No. 12. Development of left ventricular hypertrophy curve, type III.

A. Electrocardiogram from 21 nov. 1936.

B. Electrocardiogram from 26 juni 1943.

No. 91. Development of left ventricular hypertrophy curve, type III.

A. Electrocardiogram from 24 dec. 1937.

B. Electrocardiogram from 24 sept. 1943.

No. 64. Regression of left ventricular hypertrophy curve, type III. (?)

A. Electrocardiogram from 16 nov. 1936.

B. Electrocardiogram from 12 aug. 1943.

the cardio-thoracic index still remained normal, (she had previously had a drop heart), now presents a characteristic Type III electrocardiogram. Consequently the electrocardiogram here is of greater clinical import than the single röntgenogram.

In the five patients who got angina pectoris during the observation period the electrocardiogram is unaltered in 2 cases (one normal and one of Type III). One of the five has got infarction in addition to Type III and in two the electrocardiogram has developed from normal to Type III of left ventricular hypertrophy. Among the three patients whose angina pectoris has disappeared two continue to have a normal electrocardiogram, while in one it has developed from normal to a hypertrophy curve of Type II. Thus we also here find no certain connection between the left

ventricular hypertrophy curves and the angina pectoris syndrome. Only one patient, with chronic cardiac insufficiency, got auricular fibrillation.

Proteinuria supervened in two patients, in one of whom there developed nephro-sclerosis. In six cases a previously present intermittent proteinuria has now disappeared. The renal function is distinctly reduced, to the insufficiency stage, in two cases (Table 10). Patient No. 2, b. 1875, woman, with standard clearance of 67 per cent in 1936, is now found to be free from clinical symptoms, but with standard clearance of 16 per cent, proteinuria, concentration test to specific gravity 1013. In Patient No. 19, woman, b. 1869, the standard clearance has fallen from 29 to 12 per cent, with considerable hyperazotemia. Here, however, we have a chronic pyelonephritis with renal calculi. In six patients there is a doubtful reduction of the renal function. (*Example: No. 82, with maximum clearance 91 per cent in 1937, in 1943 maximum clearance 44 per cent, concentration test to 1018.*) In three cases the renal function shows doubtful improvement. In 26 patients the renal function is undoubtedly normal (4 were not satisfactorily examined). As regards the ophthalmoscopic findings, a considerable arteriosclerosis has supervened in 10 cases, while in 2 cases a previously existing papillary edema has now disappeared. A rather severe retinopathy has arisen in one patient with diabetes.

### Discussion.

In 13 cases, or 26 per cent, of the 50 with known cause of death, death was due to cardiac insufficiency, in 9 cases, or 18 per cent, to myocardial infarction, thus making together 44 per cent of cardiac deaths. 19 deaths, or 38 per cent, were due to apoplexy, and at most three (6 per cent) were due to uremia. This distribution accords well with earlier findings. Janeway (4) found in 32.6 per cent »gradual cardiac death», in 40.8 per cent »uremia + apoplexy», in 10 per cent »angina pectoris». Bell and Clawson (1) found that 49.3 per cent died of myocardial insufficiency, 11.1 per cent of coronary disease, 19.3 per cent of apoplexy and 8.6 per cent of uremia. Fahr (3) says that 50—55 per cent die of cardiac diseases, 35—40 per cent of apoplexy and 10 per cent of uremia.

What is of most interest here is the extent to which we can prognosticate the death of these patients and the cause of death. Broadly speaking, it may be said that most deaths occur among those with the highest systolic and especially diastolic pressures, as well as those with enlarged hearts and with electrocardiograms showing marked left ventricular hypertrophy and among those with constant proteinuria and considerable changes in the eye-ground. Death from uremia and from myocardial infarction seems difficult to prognosticate. These deaths show no constant relation either to blood pressure, size of heart, electrocardiographic changes or renal function. Death from uremia, however, shows a certain degree of connection with changes in the retina. Death from myocardial infarction shows, and this is especially interesting, little relation to the electrocardiogram of left ventricular hypertrophy, and also comparatively little relation to angina pectoris, seeing that only three of the sixteen patients with angina pectoris had got infarction. This is in accordance with Davis and Klainer's finding (2) of less marked coronary changes in hypertensive than in non-hypertensive angina pectoris.

Death from cardiac insufficiency is found to occur equally often with low and with high blood pressure, perhaps oftener with low, but the frequency distinctly increases with increasing size of heart, which was to be expected, and with increase in electrocardiographic signs of left ventricular hypertrophy, which is perhaps of equally great interest. Deaths from apoplexy show relation to the changes in the retina of the eye, but first and foremost to the degree of systolic and especially diastolic hypertension. Every increase in the number of deaths, passing from blood pressure group I to group II and III, is due to the mortality from apoplexy. About one-third of the patients with systolic pressure above 200 and more than one-third with diastolic pressure over 125 seem to be liable to die of apoplexy within a few years. This finding must be regarded as an important point when it is a question of operative treatment. Hypertension is reckoned as an etiological factor for apoplexy in from 90 to 98 per cent of the cases. When patients with such degrees of blood pressure have a 33 per cent chance of death from apoplexy within some few years, there should here be a specially good field of indication for surgical treatment of blood pressure, as *the operative treatment will then be a prophylactic measure against death from*

*apoplexy*. It is, however, a hitherto unsolved question whether the operative treatment is capable of reducing the blood pressure in general, and especially the intracranial pressure, in sufficient degree and long enough to attain this result. Here may be mentioned Peet's figures (5). Of 350 patients operated 31, or 10 per cent, died of apoplexy. Peet's time of observation, however, was shorter, while the condition of his patients was doubtless of graver character than in our investigation.

While a mortality of 52 per cent in the course of 6 years gives a rather dark picture of the prognosis in hypertension, yet the total impression we get from re-examination of 39 out of the 44 survivors, including 36 women, is considerably brighter. Thirty-one of them must be said to have had a relatively untroubled existence and twenty must be regarded as capable of work to the extent their age permitted. Among the 8 severely affected and largely invalided patients there was 1 with cardiac insufficiency, 3 with angina pectoris, 2 with apoplectic sequels, 1 with uremia and 1 with severe hypertensive encephalopathy.

Re-investigation of the blood pressure shows that the hypertension only in some few cases displays a progressive tendency, since it can be regarded as increased only in 5 patients. Most often it is stationary and in one-fourth of the patients distinctly reduced, while in 2 patients it has become normal.

While the height of the blood pressure does not rise, the complications due to blood pressure continue to progress, although not at all rapidly. Only in 6 out of 26 cases where roentgenograms could be compared there is an undoubted increase in heart size. Especially significant is the fact that 23 of the 39 roentgenograms have on control examination received the designation «normal heart size». It is regarded as certain, however, that there has arisen a left ventricular hypertrophy, but little or no dilatation. Characteristic in this respect is Patient No. 12, who in 1936 had a drop heart and in 1943 a considerably enlarged heart, but still within normal limits. The electrocardiogram, on the other hand, was normal in 1936, but in 1943 showed a left ventricular hypertrophy curve.

The importance of the left ventricular hypertrophy curve as a diagnostic and prognostic sign in this disease is clear from the fact that 10 patients, or one-fourth of the total number, have developed (7) or further developed (3) such curves. A comparison be-

tween size of heart and electrocardiogram it was unfortunately not possible to carry out in full, but in three of the seven patients who previously had normal electrocardiograms, and now show left ventricular hypertrophy curves, there is an undoubted increase in size of the heart. The connection between this development and angina pectoris is rather loose, seeing that, while two of these patients also got angina, one of them has no longer this syndrome. Six patients who for 7—9 years have had pronounced hypertrophy curves are still living. Seventeen patients, or more than half of the total number, continue to have an entirely normal electrocardiogram, which fact also proves the great ability of the myocardium to tolerate increased work imposed upon it.

A fine example of development from essential hypertension to nephrosclerosis is furnished by Patient No. 2. In 1936 she had no proteinuria, standard clearance 67 per cent and concentration power to 1024. In 1943 she had proteinuria, standard clearance 16 per cent, blood-urea 89 and 123 mg per cent and concentration power to 1013. She was little troubled by the disease and had not consulted a doctor.

Twenty-six of the thirty-five patients examined had entirely normal renal function.

The re-investigation shows that among the survivors, apart from troubles due to chronic hypertensive encephalopathy and cerebral arteriosclerosis, it is chiefly the heart that is affected. Some patients have infarctions, some angina pectoris, in some the electrocardiograms, and to less extent the roentgenograms, show the quiet development of the hypertensive heart disease, which clinically is often still latent. In so far it may be deemed justifiable to say that the hypertension first attacks the cerebral vessels, causing apoplexy, then the heart and only in the last instance the kidneys.

### Summary.

One hundred hypertensive patients, investigated in 1936—1938, were re-examined in 1943, with a special view to the prognostic value of the earlier pathological findings in the cardio-vascular and renal systems.

52 per cent have died, 44 per cent are still living and 4 per cent have not been traced.

The causes of death are: cardiac insufficiency in 26 per cent, myocardial infarction in 18 per cent, apoplexy in 38 per cent and uremia in, at most, 6 per cent.

While myocardial infarction and uremia are difficult to prognosticate, as they show no distinct relation to the earlier findings in the cardio-vascular and renal systems, cardiac insufficiency exhibits a distinct correlation to the size of the heart and to the electrocardiographic development (left ventricular hypertrophy), and the apoplexies show especially clear relationship to the height of the blood pressure, both the systolic and particularly the diastolic. Nearly one-third of those with systolic pressure above 200 mm Hg and more than one-third of those with diastolic pressure above 125 died of apoplexy during the observation period.

The operative treatment of hypertension may in these groups be regarded from the standpoint of *prophylaxis of cerebral hemorrhage*.

While in one patient there has developed nephrosclerosis, the 39 patients re-examined show primarily a slow development of hypertensive heart disease, sometimes with myocardial infarction and angina pectoris, sometimes with cardiac enlargement, this disease being electrocardiographically characterized by development of left ventricular hypertrophy in different stages.

#### Literature.

1. Bell, E. T. and Clawson, B. J.: Arch. of Path. 1928: 5: 939. —
  2. Davis, D. and Klainer, M. J.: Am. Heart J. 1940: 19: 198. — 3. Fahr, G.: Am. J. Med. Sc. 1928: 155: 453. — 4. Janeway, Th.: Arch. Int. Med. 1913: 12: 755. — 5. Peet, M. M., Woods, W. W. and Spencer Braden: J. Am. Med. Ass. 1940: 115: 1875. — 6. Rasmussen, H. and Thingstad, R.: Acta Med. Scand. 1939: 101: 237. — 7. Rasmussen, H.: The Electrocardiogram in Aortic Insufficiency. Acta Med. 1944: 118: 385.
-



From the University Institute of Medical Anatomy, Copenhagen (Chief: Professor Harald Okkels, M. D.) and the »Medicinalco» Laboratory of Biochemistry, Copenhagen (Chief: Erik Jacobsen, M. D.)

## On the Importance of the Duodenal Glands of Brunner to the Formation of red Blood Corpuscles in Swine.

By

C. L. S. BOHN, E. LANDBOE-CHRISTENSEN and C. M. PLUM.

(Submitted for publication June 28, 1944).

---

In a previous communication on the topographical aspects of the Brunner glands in swine (Landboe-Christensen and Bohn, 1944) attention was drawn to the possibility of utilizing the peculiar glandular arrangement to ascertain the possible significance of the Brunner glands to the formation of the antipernicious anemic principle. Accordingly, experiments have been carried out in which the proximal (oral) part of the duodenum, containing the bulk of the Brunner glands, was operated upon. The present publication is a preliminary report on the effect of such experiments upon the formation of red blood corpuscles.

We have used two young swine of Danish domestic race, about 2 months old and weighing from 12 to 22 kilograms. The animals were anaesthetized by injections of sodium phenylethylbarbiturate. Postoperative intramuscular injections of 1 gram sulphathiazole in aqueous solution were given for prophylactic reasons.<sup>1</sup>

---

<sup>1</sup> We want to express our gratitude towards chief pathologist of the Copenhagen Municipal Hospital, Svend Petri, M. D., whose large experience concerning experimental surgery on swine was placed at our disposal. Likewise we want to thank our colleague Ole Gottlieb of the Institute of Medical Anatomy for his valuable assistance during the operations.

In one swine the duodenum was severed distally to, but very near, the place where the bile duct pierces the gut; and again immediately before (proximal to) the opening of the pancreatic duct. Care was taken to avoid vascular lesions in the mesoduodenum. Thus an isolated duodenal pouch of 6 cm's length was formed, the proximal end of which was closed by a double purse-string suture. Into the distal end was tied a double-collared tube piercing the abdominal wall through an incision lateral to the laparotomy wound. The continuity of the remaining upper and lower duodenal parts was secured by making an end-to-end anastomosis. The secretion from the duodenal pouch was collected in small rubber receptacles which were successively fitted to the tube.

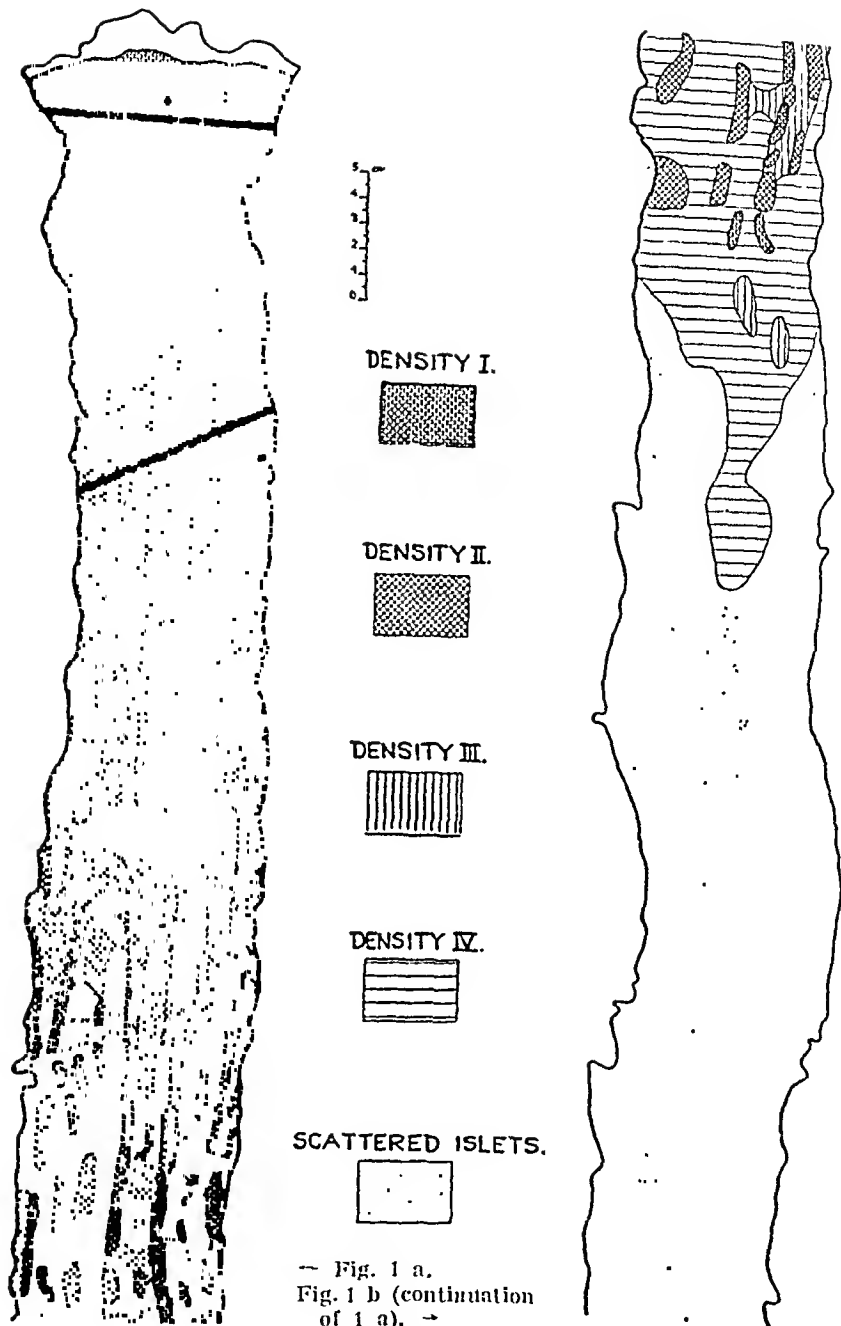
The secretion was tested for a possible content of the reticulocyte-ripening principle according to the technique devised by Plum (1944). These tests showed that the reticulocyte-ripening index of the duodenal secretion collected (conf. table 1) was of nearly the same magnitude as the corresponding index for gastric juice in man (conf. Plum, 1944); moreover, it equalled the index found by us in samples of gastric juice from swine.

Table 1.

Secretion from the duodenal pouch in swine No. 1. (The ciphers in italics indicate the reticulocyte - ripening index after activation with 0.1 cm<sup>2</sup> of a 0.1 per cent tyrosine solution.)

Date	March 21 —	March 22 —	March 23 10 <sup>15</sup> to 11 <sup>30</sup>	March 23 11 <sup>30</sup> to 13 <sup>30</sup>	March 24 10 <sup>10</sup> to 11 <sup>00</sup>	March 24 11 <sup>00</sup> to 13 <sup>00</sup>
pH .....	—	—	8.1	8.1	8.0	8.2
desiccated matter per cent.....	—	1.10	1.25	1.05	1.23	1.33
ripening- index of secretion..	0.18/0.60	0.16/0.78	0.14/0.68	0.18/0.64	0.14/0.60	0.14/0.64

Like the pyloric glands — but contrary to those of fundus — the duodenal glands secrete continually (Panomarew; Florey and Harding). From our duodenal pouch (fig. 1), which we estimate to contain about half the total amount of Brunner glands, we were able to collect such quantities of juice corresponding to a rate of secre-



— Fig. 1 a.  
Fig. 1 b (continuation  
of 1 a). —

(Landboe-Christensen & Bohn 1944).

Map of the extent and density of the Brunner gland area in a 6 months old swine. The comparative length of duodenum in 6 months and 2 months old swine is in proportion 1 to 1, the relative densities and type of distribution being the same. The part of duodenum indicated by the two transversal lines was either isolated (as in swine No. 1) or excised (swine Nr. 2). The two black spots on the map indicate the outlet of the bile duct (the proximal) and the outlet of the pancreatic duct.

*Density I* signifies: Glandular islands packed so closely that the average width of the interglandular intervals does not exceed the average diameter of the islands.

*Density II*: The interglandular intervals are wider than the islands but not more than twice as wide.

*Density III*: On an average the interglandular intervals are wider than twice, but not three times the diameter of the glandular islands.

*Density IV*: The intervals exceed more than three times the diameter of the islands; still the islands are numerous enough to speak of a fairly equal distribution: a continuous pattern.

*Scattered islands*: Larger and variable intervals between the islands.

Table 2.

Hematological findings in swine No. 1 with duodenal pouch.  
(The ciphers in italics indicate the reticulocyte-ripening index after activation with 0.1 cm<sup>3</sup> of a 0.1 per cent tyrosine solution.)

Date	March 29	April 12	April 21
hemoglobin per cent .....	62	60	70
erythrocytes (millions) .....	4.8	5.1	5.4
reticulocyte per cent .....	1.6	1.7	1.9
leucocytes .....	12,000		9,500
ripening-index of plasma .....	0.71/0.83	0.72/0.86	0.71/0.86

tion of about 5 cm<sup>3</sup> per hour during the day. Owing to the difficulty of devising a receptacle of suitable capacity we found it impossible to collect the nightly secretion. As it is, the organism is deprived of very considerable quantities of secretion. A thorough hematological examination of the swine was therefore indicated. The results are tabulated in table 2.

The reticulocyte percentage in the blood from swine No. 1 is definitely higher than normal (Wirth, 1931: 0.3—0.4 per cent; Plum, 1944 0.4—0.8 per cent). The ripening-index is below the mean value hitherto considered normal (Plum, 1944: 0.81), and the haemoglobin percentage is low. Special attention should be drawn to the fact that the ripening-index of plasma is capable of activation by tyrosine. This phenomenon does not occur in normal animals. On the other hand it has been produced in rabbits after blockade of the reticulo-endothelial system (Jacobsen and Plum, 1943). Likewise the phenomenon has been observed in patients suffering from pernicious anaemia or Graves' disease as well as certain gastric anomalies (Ruth Plum, 1943).

Encouraged by these findings we decided to extend our experiments by operating yet another animal. It was of the same litter as swine No. 1, but one month older and weighing 22 kilograms. After previous hematological examination (table 3) we resected the part of the gut corresponding to the duodenal pouch of swine No. 1. The length of the excised gut was 7 cm. It was cleared and stained by the Landboe-Christensen-method (fig. 2). After the operation the hematological examinations were continued (table 3).

Table 3.

Hematological findings in swine No. 2 before and after partial duodenectomy (The ciphers in italics indicate the reticulocyte-ripening index after activation with 0.1 cm<sup>2</sup> a 0.1 per cent tyrosine solution.)

Date	March 29	April 12	April 17	April 21	May 2	May 10	May 19
hemoglobin			O				
per cent ....	95	89	P	68	60	55	56
erythrocytes			E				
millions) ..	7.6	8.1	R	5.1	5.0	4.9	4.8
reticulocyte			A				
per cent ....	0.4	0.5	T	2.2	4.0	5.4	4.2
leucocytes ..	9,600		I	12,800	10,800	12,800	18,600
ripening-in-			O				
dex of plasma	0.86/0.88	0.85/0.86	N	0.68/0.86	0.68/0.82	0.65/0.82	0.64/0.

The tabulated findings show that a marked rise in reticulocyte percentage occur both in the case of isolating a duodenal pouch and in the case of partial duodenectomy. The rise cannot be caused by any regeneration of erythrocytes resulting from the hemorrhage, because the loss of blood during the operation was very slight, at most about 10 cm<sup>3</sup>. Besides, anæmic conditions of the posthemorrhagic type are characterized by a rise in reticulocyte percentage as well as in the ripening-index of plasma (Plum, 1944) whereas we have found the index definitely lowered in our experiments. The hematological changes cannot be caused by any toxic influence from the anaesthetics employed because another swine, which was anaesthetized and treated with sulphathiazole like the operated animals, did not develop any hematological changes.

It should be noted that in addition to the hematological changes the swine with the duodenal pouch has undergone a marked retardation of growth. It weighed 12 kilograms just before the operation; two months later it weighed only 13 kilograms. Another animal of the same litter, kept beside swine No. 1 in the same sty, fed and looked after in the same way, weighed at the same time 22 kilograms. This animal (swine No. 2) then had part of its duodenum removed and since then it too has shown retardation of growth. At 33 days after the operation it weighed only 23 kilograms in spite



Fig. 2. Mucous membrane from the removed part of duodenum in swine No 2. Photography in transillumination showing the density and grouping of the Brunner glands.

of good appetite and normal excrements. No symptoms of stenosis were observed.

Therefore, we feel justified in assuming that the peculiar hematological findings must be due to a deficiency caused by the parti 1 removal of duodenal secretion. In swine No. 1 the proximal (oral) part of duodenum, rich in glandular parenchyma, is isolated and the secretion deprived the organism; in swine N. 2 the corresponding part is excised. The difference between the findings in the two cases may indicate that not only the secretion, but the duodenal wall in itself, may be a decisive factor in regard to the formation of red corpuscles.

At the present state of our investigations a large number of pro-

blems emerge from the observation based on our experiments: that the duodenal secretion plays a role in blood formation.

One of the rather puzzling problems is why the removal of what we estimate to be about half the duodenal specific parenchyma causes such massive alterations in the blood and otherwise. It is unusual, indeed, to observe in experimental biology a state of grave deficiency resulting from suppression of only one half of any glandular mass. A comprehensive research program is in progress in order to define the biological mechanism by which the interrelationship between duodenal secretion and red bone marrow is brought into play.

In bringing the present communication to its close, we want to point out, that in two operated swine we have deprived the animals of part of their duodenal secretion. Both animals developed peculiar hematological changes, and we assume that this effect is caused by the duodenal deficiency, particularly the loss of a reticulocyte-ripening principle contained in the duodenal secretion. That this secretion predominantly is a product of the Brunner glands is exceedingly probable; surely the large amount of the secretion favours such an assumption.

### Summary.

Increase of reticulocyte percentage and decreased ripening index of plasma was observed in two swine in which the part of duodenum placed between the openings of the bile duct and the pancreatic duct was either isolated or excised.

### References.

1. Babkin, B. P.: »Die äussere Sekretion der Verdauungsdrüsen». I Auflage; Berlin; Jul. Springer, 1928. — 2. Florey, H. V. & H. E. Harding: »Function of Brunner's glands and pyloric end of stomach». *Path. & Bact.* 37: 431, 1933. — 3. Florey, H. V. & H. E. Harding: »Further observations on secretion of Brunner's glands». *Path & Bact.* 39: 255, 1934. — 4. Jacobsen, E. & C. M. Plum: »The rôle of the reticulo-endothelial system in the ripening of reticulocytes». *Acta physiol. Scand.* 5: 1, 1943. — 5. Landboe-Christensen, E.: »The duodenal glands of Brunner in man, their distribution and quantity». Copenhagen: E. Munksgaard. London: Humphrey

Milford. 1944. Dissert. Acta path. et microbiol. Scand. Suppl. LII. — 6. Landboe-Christensen, E. & C. L. S. Bohn: »Topographical aspects of the Brunner glands in swine». Acta path. et microbiol. Scand. Suppl. LIV. 1944. — 7. Panomarew: St. Petersburg 1902. Dissert. Quoted from Babkin. — 8. Plum, C. M.: »Undersøgelser over Reticulocytmodninger in vitro». København: Arnold Busck, 1944. Dissert. — 9. Plum, R.: »Reticulocytmodnende Stoffer hos syge og sunde». Ugesk. f. Læger 105: 1173, 1943. — 10. Wirth, D.: »Grundlage einer klinischen Hämatologie der Haustiere», Wien: Urban & Schwarzenberg, 1931.

---



(From the Institute of Physical Chemistry and the Department of Hyg and Bacteriology, University of Upsala, Sweden.)

## Distribution of Poliomyelitis Virus in the Intestines of Normal Mice.

By

SVEN GARD.

(Submitted for publication October 17, 1944).

In 1929 Kling (4a) advanced a theory according to which human poliomyelitis were a water-borne disease. The portal of entry of the infection were to be found not in the nasal mucous membranes but in the alimentary tract, preferably the intestines. The virus gained access to the organism with contaminated water and food. This theory, at the beginning rather coolly received and still far from generally accepted, has been substantially corroborated on important points in later investigations by a number of authors, including Kling himself.

For instance, Sabin (19, 20, 21) and Howe and Bodian (3), in virological and anatomical studies, presented evidence to show that the virus in migrating through the central nervous system (CNS) followed certain pathways, preformed and well defined, principally the neural tracts. It was, therefore, possible, in early stages of the infection, to trace the origin of the pathological process by studying the distribution of lesions. It was found, in the majority of cases, a histological picture indicating that the virus had entered through the spinal roots, in cases of acute bulbar paralysis through *N. vagus* or *glossopharyngeus*, but never by way of the olfactory nerves. These findings seem to rule out the nasal mucous membrane

as a portal of entry and, consequently, droplet infection as a principal factor in the epidemiology of the disease. On the other hand, they are not incompatible with Kling's theory, although entrance through the spinal roots might ensue from intracranial as well as intestinal infection.

Furthermore, by means of the ether treatment, instituted in poliomyelitis research by Paul and Trask (25), it has been possible to demonstrate, in conformity with previous observations by Kling, Pettersson and Wernstedt (8), the presence of virus in stools and intestinal contents in a high percentage of paralytic and non-paralytic cases as well as in healthy persons resident within epidemic areas (7, 9, 10, 13a, 16, 17, 26). As pointed out by Paul and Trask, the ease with which the virus can be detected in this kind of material as compared with the difficulty to demonstrate its presence in nasopharyngeal washings suggests that the virus is present in the intestines not only more regularly but also in considerably larger amounts than in the nasopharyngeal cavity. In this connection it should be emphasized that, actually, the virus was never demonstrated in pure nasal washings. All instances in the literature deal with combined nose and throat washings or throat washings alone. There exists, thus, no evidence of the elimination of the virus with nasal secretions but abundantly so of the excretion with the feces.

Consequently, it is not amazing that virus could be detected in urban sewage during epidemics of poliomyelitis (4b, 13b, 14, 15). The apparently large quantities of virus thus detected were, however, remarkable as compared with the small number of cases observed in the areas concerned and the enormous dilution of the material considered. As a possible explanation one must assume either the existence at the time of a great number of healthy carriers or else a multiplication of the virus in the sewage. --- Kling also succeeded in demonstrating the presence of the virus in a sample of well water (4c) and in butter (4d), both suspected of contamination with sewage and considered as possible sources of infection.

As, however, the epidemiology of poliomyelitis cannot be explained simply in the same way as the water-borne typhoid fever through dissemination of virus from healthy carriers, water serving only as a vehicle, Kling has been looking for an interne-

diate host of some kind. Out from the observations on the presence of virus in sewage and assuming that the high virus content can be accounted for only by an actual multiplication of the virus excreted he concludes that a sewage microorganism must be responsible. For certain reasons he has concentrated on a coprozootic protozoon of the species *Bodo*, not infrequently found in the human intestines. Certain circumstantial evidence supporting this hypothesis has been produced but the crucial test, demonstration of virus in the protozoon, is still lacking (5, 6).

From somewhat different points of departure the present writer, studying mouse poliomyelitis (Theiler's disease 23), arrived at a similar conclusion (b). On electron micrographs of purified preparations the virus appeared in the shape of slender rods or filaments. The virus particles resembled strikingly those of certain plant viruses. Among animal viruses, on the other hand, otherwise notoriously symmetrical in shape, this morphological type was completely unprecedented. One might suspect, therefore, that the real host of the virus does not belong among the warm-blooded animals, although certain strains or modifications of the virus are capable of propagating also in the CNS of a number of mammals.

Olitsky (12a) showed that the virus of mouse poliomyelitis was present in the intestines of normal mice. He found that newborn and young suckling mice were always virus-free. In mice at the age of 2 weeks it was occasionally detected. From then on the frequency of positive findings increased and at the age of 5—7 weeks practically 100 p.c. of the animals were harbouring the virus in their intestines. This important observation was confirmed by Theiler and Gard (24) who studied also the gross distribution of the virus in the alimentary tract. They were unable to detect any virus in the mouth, throat and oesophagus. Occasionally small amounts were found in the stomach contents but never in the wall of the stomach. It was almost constantly present in the intestinal contents and also in the intestinal wall, rinsed in running tap water. Olitsky (12 b), using a more rigorous method of rinsing the gut, repeated shaking with saline in a shaking machine, was unable to detect any virus in the intestinal wall. Histological examination of the gut revealed a considerable damage of the mucous membrane after this violent treatment, whereas the method employed by Theiler and Gard left large amounts of the contents still sticking

to the mucosa, especially in the crypts. It must be left undecided, therefore, whether the virus was actually present in the superficial layer of the mucous membrane or in the intestinal contents exclusively. The virus being otherwise exquisitely neutrotropic as far as the distribution in the mammalian host is concerned, an assumption of its presence within epithelial cells cannot be accepted without further confirmation. *A priori* it would seem more likely that the virus appearing in the «wall» preparations originated from adherent intestinal contents rather than from the mucous membrane proper. In that case, obviously, the intracellular habitat of the virus being beyond doubt, one must further assume an intestinal microorganism as a host of the virus.

Concerning the type of organism to be looked for in this respect nothing but vague hints can be offered at present. There is only one class of microorganismal viruses so far studied, i.e. the bacteriophages. These appear as spherical or ellipsoidal bodies never even remotely resembling the poliomyelitis virus. It seems hardly probable, therefore, that a bacterium would serve as a host of the virus. The characteristic morphology points undoubtedly towards a plant of some kind, possibly a fungus. However, on account of lack of information it is impossible to decide whether a fungus, a protozoon, or a helminth is the most probable host. Some recent observations (1, 11) tend to show that protozoans are sometimes attacked by virus diseases, although the nature of the infectious agents is not yet studied. It is worth remembering also in this connection that in one instance, well documented (22), a helminth serves as an intermediate host of an animal virus, i.e. the lung worm transmitting swine influenza.

The mouse seems to be an ideal object of research for the elucidation of this problem. It should be possible to study closely the gradual invasion of the intestinal tract by different microorganisms following the change of diet towards the end of the suckling period, and find out whether or not a correlation exists between the appearance of the virus and that of a certain microorganism. Preliminary to a study of that type, however, the above mentioned observations of Olitsky and of Theiler and Gard should be confirmed. The latter item is the object of this paper.

Table II.

material	—log conc.	no. in- oculated	number becoming paralyzed after days																														y
			7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30							
contents	1	10	1		1	1	1	1		2					3															.077			
	2	10					1	1	1		1						2	1	1			1								.052			
	3	10								1	1			1	1			2	2											.044			
	4	10												1						1										.011			
	5	10																												.000			
wall	1	10							1	1					1					1									1	.028			
	2	10																		1										.005			
	3	10																												.000			
	4	10																												.000			
	5	10																												.000			

see 2b). By calculation of the numerical value of  $b$  from the 6 experiments the following figures were obtained (table III). As there seems to be a significant difference between the two series of titrations, it was deemed advisable to use different  $b$  values in calculating the titers of ingesta and the wall, viz. the mean values obtained, 0.030 and 0.022 respectively.

In table IV the log activity values are listed, calculated in accordance to the different methods mentioned, together with the differences in activity between ingesta and intestinal wall for each experiment. The table shows that the activity of the intestinal contents with one single exception (exp. 3, incubation time titer) was higher than that of the intestinal wall. The differences observed are statistically significant for the 50 p.c. endpoint methods and almost significant for the incubation time method. The amount of contents obtained from one specimen averaged 0.6 g; the weight of the washed intestinal wall was an average 1.0 g. This means that the viral activity of the ingesta represents 80 p.c. (titration method c) to 90 p.c. (titration method a) of the total activity of the small intestines. These are minimum figures as part of the ingesta was lost by washing the intestinal wall.

*Presence of virus in different levels of the small intestines.* In another series of experiments the presence of virus in the duodenum was studied. The small intestines were divided into two portions. One consisted of the proximal 2—3 cm with contents, the other

Table III.

experiment	numerical value of b	
	contents	wall
1	0.031	0.021
2	0.037	0.018
3	0.031	0.028
4	0.031	—
5	0.030	0.018
6	0.021	0.023
mean	0.0302	0.0216
difference	0.0086 $\pm$ 0.0028	

comprised the remainder. The specimens were ground separately with sand and saline, 2 ml to the former, 5 ml to the latter portion. After centrifugation and etherization the extracts were inoculated in 0.02 ml amounts into groups of 4 weeks old mice. The results of these infectivity tests are listed in table V.

In experiment 4 none of 20 animals inoculated were paralysed and none were subsequently immune. In experiment 12 none were paralyzed but two were immune when tested after 4 weeks. In the remaining experiments each group showed paralyzed animals. Thus, of 15 animals tested at least 13, probably 14 were carrying virus in the intestines and 12 of these showed the presence of virus in the duodenum. The percentage figures suggest that the virus con-

Table IV.

Exp.	50 p. c. morbidity			50 p. c. mortality			Incubation period		
	cont.	wall	diff.	cont.	wall	diff.	cont.	wall	diff.
1 .....	3.4	2.6	0.9	2.9	2.3	0.6	3.3	3.1	0.2
2 .....	2.2	1.4	0.8	1.7	1.2	0.5	2.3	1.8	0.5
3 .....	2.8	2.5	0.3	2.5	2.0	0.5	3.1	3.3	-0.2
4 .....	2.1	0.0	2.1	1.5	0.0	1.5	2.2	0.0	2.2
5 .....	2.8	2.1	0.7	2.8	1.3	1.5	2.9	2.2	0.7
6 .....	3.5	1.0	2.5	2.3	0.5	1.8	3.0	1.2	1.8
mean diff.	1.21 $\pm$ 0.36			1.07 $\pm$ 0.24			0.86 $\pm$ 0.38		

Table V.

experiment no	percentage of paralyzed and immune mice	
	duodenum	jejuno-ileum
1	80	86
2	100	100
3	80	100
4	0	0
5	0	14
6	90	90
7	40	80
8	80	100
9	100	100
10	40	40
11	100	100
12	0	20
13	100	100
14	100	90
15	10	20
mean	63	70

e

centration in the uppermost part of the small intestines is somewhat lower than it is further down, although this is by no means certain as the extracts were not prepared on a weight by weight basis. For practical purposes it can, obviously, be assumed that the virus, when present at all, is also to be found in the most proximal part of the intestines.

### Discussion.

The nature of our problem necessitates a study on a quantitative basis. The amounts of virus present in different fractions of the specimens must be evaluated. This can be done only by measuring the biological activities. An infectivity titer is, however, of a very limited value as a measure of the virus content. It represents simply the number of minimum infective dose (MID) present. The unit 1 MID does not correspond to a fixed number of virus particles or a fixed amount of virus protein, it varies with the virulence of the strain of virus and the resistance of the test animals. In an extensive study on the theory of titration (2b) it was found that

the slope of the titration curve, too, was dependent upon these two qualities. Thus, the coefficient of regression,  $b$ , might be said to be a numerical expression of the quotient virulence: resistance. The higher the virulence or the lower the resistance, the steeper the slope of the titration curve, and *vice versa*.

By a partial inactivation of a certain virus preparation the titer is lowered but the slope of the titration curve does not change, the value of  $b$  is not affected. Thus, treatment with alcohol or acetone, oxidizing agents, acids, heavy metals, and heat or desiccation *in vacuo* does not alter the specific character of the strain of virus, as manifested in its virulence. The effect is simply equal to a dilution of the material.

Therefore, a change in the slope of the titration curve signals one or both of two possibilities: either a «mutation» of the virus or an influence upon the resistance of the host. In a recent paper (2c) a phenomenon of the latter type was described. Certain tissue components from immune animals were found to afford protection against experimental infection. No combination with the virus or reaction of any kind could be demonstrated *in vitro*. In animals thus protected the slope of the titration curve was distinctly diminished, leaving but one explanation possible: the resistance of the animals increased by administration of these tissue components. It should be emphasized that differences of this type can hardly be evaluated by means of an analysis of 50 p.c. endpoint titers, unless the material available is exceedingly large.

In the present case a question of a similar type arises. We have two kinds of material in which the strains of virus present must be in all probability identical, and yet there are differences in the slope of the titration curves. If these differences prove significant, which is far from certain, the number of observations so far being too small, it must be assumed that the tissues of the intestinal wall contain a factor, influencing the resistance of the test animals. *A priori* this assumption is plausible enough. In that case the titer values obtained are not directly comparable and great caution must be exercised in evaluating the actual amounts of virus present. Obviously further studies are necessary to elucidate this point.

Let us suppose that, in further experiments, the difference in regression of the titration curves observed will be found significant. In that case the «wall» titers will appear too low and a correction



has to be added. A study of the variation of titer value and regression in animals of different resistance has revealed that this correction will probably not exceed 0.4 units of log activity. This still leaves a difference between »contents» and »wall» of at least 0.1 units, meaning that approximately 70 p.c. of the total virus content were to be found in the ingesta. This figure represents, obviously, an absolute minimum.

Subjecting the conditions of the experiments to a closer analysis we find the following points of interest. As already pointed out part of the intestinal contents is lost during the preparation of the specimens. Another fraction is retained in the crypts of the mucous membrane. Furthermore, as virus is almost constantly present in the mesenteric lymph nodes, indicating a continual absorption and transportation by way of the lacteals, one must expect to find a certain amount of virus in the intercellular spaces and the lymph capillaries of the mucosa.

It is obvious, therefore, that the figures computed from the titer values obtained are not representative of the real distribution of virus. On one hand, the absolute quantity of virus in the ingesta is higher than indicated by the experimental results. On the other hand, the amount of virus detected in preparations of the intestinal wall includes the fraction from the ingesta, retained in the crypts, and the intercellular virus in the lymph spaces, both of which are of no interest in the present connection. It is impossible to estimate, with any degree of certainty, the exact amount of such accessory virus but it should be safe to assume that the virus present in the interior of intestinal tissue cells might amount to a few percent of the total at most.

The accumulated experience from tissue culture of different viruses tends to show that the concentration of virus is regularly higher in the tissue than in the surrounding liquid phase. Only when extensive disintegration of host cells occurs, as in complete lysis by bacteriophage, the reverse is true. There is no indications of any remarkable cytolysis in the intestinal tissue of animals harbouring poliomyelitis virus in the gut. On the condition that virus reproduction were localized to the mucous membrane one would expect, therefore, to find the major part of the virus in the tissue phase. Therefore, the evidence now presented is contrary to the assumption that the virus is propagating in the mucous membrane proper.

Incidentally table IV may serve to illustrate another point of interest, *viz.* the enormous quantities of virus that are excreted with the feces. The total amount of virus in the small intestines can be estimated at an average of about 100,000 MID. Considering the rapid passage of the ingesta through the gut the 24 hours excretion of virus can be estimated at about 1 million MID, for several weeks in succession. During the acute stage of poliomyelitis, when the concentration of virus in the CNS has attained its maximum, the total quantity of virus present in brain and spinal cord amounts to about 10,000 MID<sup>1</sup>. Thus, the amount of virus excreted daily by perfectly normal and healthy animals is 100 times greater than the total virus content of the CNS of mice attacked by the disease. If the same relative figures are applicable to human poliomyelitis a carrier rate of 0.15 p.c. of the population would suffice to account for the detection of virus in urban sewage. As, in a number of investigations, considerably higher carrier rates have been found it seems unnecessary to assume a multiplication of virus in the sewage as an explanation of the positive findings.

If the conclusions concerning the distribution of virus in the intestines are correct a systematical search for an intermediate host of a microorganismal nature is strongly indicated. The results of the latter part of the experiments now reported seem to facilitate a study of that kind. According to those experiments the field of observation can be restricted to the uppermost part of the small intestines. This is a great advantage as the number of species of the intestinal flora increases considerably towards the distal levels of the gut.

### Summary.

The concentration of mouse poliomyelitis virus in the ingesta and the intestinal wall of healthy mice was determined by titration in mice.

The viral activity of the intestinal contents exceeded that of the wall with about 10 times. When the special conditions of the experiments were considered it could be concluded that at most a few

<sup>1</sup> This figure refers to infections by fecal strains of moderate virulence. The highly virulent FA strain attains values of 100 millions MID or more.

per cent of the total virus content might be present in the interior of intestinal cells.

This indicates that the multiplication of virus might occur in the ingesta, presumably in a microorganism serving as a host.

The virus, when present at all, was almost constantly found also in the uppermost part of the small intestines.

### References.

- 1) Brug: *Zbl. Bakt. I Orig.* 148, 166 (1942). — 2) Gard: a) *J. exp. Med.* 72, 69 (1940); b) *Acta Med. Scand. Suppl.* 143 (1943). c) *Acta Med. Scand.* 119, 27 (1944). — 3) Howe and Bodian: a) *Proc. Soc. exp. Biol. Med.* 41, 540 (1939); b) *Brain* 63, 135 (1940); c) *Bull. Johns Hopkins Hosp.* 68, 58 (1941); d) *ibid.* 68, 248 (1941); e) *ibid.* 69, 149 (1941); f) *ibid.* 69, 183 (1941). — 4) Kling: a) *Acta Soc. Med. Suec.* 55, 1 (1929); b) *Bull. Acad. Med.* 123, 335 (1939); c) *Internat. Bull. Vol. A* 40 (1940). d) Report to the Royal Medical Board 1940. — 5) Kling, Olin and Fåhræus: *Acta Path. Microbiol. Scand. Suppl.* 54, 499 (1944). — 6) Kling, Olin, Fåhræus and Norlin: a) *Acta Med. Scand.* 112, 217 (1942); b) *ibid.* 112, 250 (1942). — 7) Kling, Olin, Magnusson and Gard: *Bull. Acad. Med.* 121, 826 (1939). — 8) Kling, Pettersson and Wernstedt: *Comm. Inst. Med. Etat* 3, 5 (1912). — 9) Kramer, Gilliam and Molner: *Publ. Health Rep.* 54; 1914 (1939). — 10) McClure and Langmuir: *Am. J. Hyg.* 35, 285 (1942). — 11) Mottram: *Nature* 147, 479 (1941). — 12) Olitsky: a) *Proc. Soc. exp. Biol. Med.* 41, 434 (1939); b) *J. exp. Med.* 72, 113 (1940). — 13) Paul and Trask: a) *J. Am. med. Assoc.* 116, 493 (1941); b) *J. exp. Med.* 75, 1 (1942). — 14) Paul, Trask and Culotta: *Science* 90, 258 (1939). — 15) Paul, Trask and Gard: *J. exp. Med.* 71, 765 (1940). — 16) Paul, Trask and Vignec: *J. exp. Med.* 71, 751 (1940). — 17) Piszczek, Shaughnessy, Zichis and Levinson: *J. Am. med. Assoc.* 117, 1962 (1941). — 18) Reed and Muench: *Am. J. Hyg.* 27, 493 (1938). — 19) Sabin: *Am. J. Dis. Child.* 60, 1313 (1940). — 20) Sabin and Olitsky: *J. Am. med. Assoc.* 108, 21 (1937). — 21) Sabin and Ward: *J. exp. Med.* 67, 201 (1938). — 22) Shope: *Science* 89, 441 (1939). — 23) Theiler: *Science* 80, 122 (1934). — 24) Theiler and Gard: *J. exp. Med.* 72, 79 (1940). — 25) Trask, Vignec and Paul: *J. Am. med. Assoc.* 111, 6 (1938). — 26) Wenner and Casey: *J. clin. Investig.* 22, 117 (1943).

(From the medical clinic of Karolinska Sjukhuset, Stockholm. Chief physician: professor Nanna Svartz, M. D. and from dep. II Kommunehospitalet, Copenhagen. Chief physician: Hans Heckscher, M. D.)

## Cardiac and Respiratory Neurosis after Contusions of the Chest-Wall.<sup>1</sup>

By

HANS HECKSCHER.

(Submitted for publication August 2, 1944).

### Introduction.

Diseases of the heart, merely functional or organic, have been seen to develop due to blunt i.e. not penetrating contusions of the thoracic wall. A thorough description of such cases where organic lesions of the heart were observed is given in a monography by Erik J. Warburg (Subacute and chronic pericardial and myocardial lesions etc. Copenhagen, 1938). Undoubtedly the war-experiences will add to our knowledge of such cases. Still it would be incorrect to suppose that traumatic cases presenting symptoms of cardiac disturbances are uncommon in time of peace. At least this holds good with regard to cases presenting merely functional disturbances. In Denmark these traumatic cases can easiest be collected from the different private and public insurance-companies.

### Grouping of cases.

A detailed examination of a number of cases collected in this way places them into three groups, although there are some border-cases. These groups are:

<sup>1</sup> Read in the swedish society of internal medicine, svensk medicinsk riksstämman, Stockholm, 27/11, 1943.

- I. *Patients suffering from undoubtedly organic lesions of the heart,*
  - a) *pre-traumatic, the heart-trouble being conspicuous even before the accident,*
  - b) *post-traumatic, the heart-trouble developing after the accident.*
- II. *Patients suffering from arteriosclerosis but presenting no signs of cardiac disease.*
- III. *Patients suffering from a traumatic neurosis which has taken the form of a cardiac and respiratory neurosis.*

Of these three categories number I is the rarest and number III the most often met with.

### **I. Post-traumatic organic disease of the heart.**

As a reference may be given to the thorough description of 178 cases of traumatic injury of the heart by Warburg (l.c.), it seems superfluous here to go into a detailed discussion of this topic. Still some cardinal points may be touched upon.

In most cases the blow seems to have been fairly violent and directed against the precordium itself or its nearest surroundings. Warburg therefore concludes that the possibility of a traumatic lesion of the heart or the pericardium must be considered unlikely if the contusions are located to other parts of the thorax.

In the majority of the cases collected by Warburg the immediate consequences of the accident were conspicuous and severe; shock, intense pains in the region of the heart, enlargement of the heart, arrhythmia and pericardial affections were often followed by signs of cardiac insufficiency. Death followed in 74 out of 178 cases, in most cases due to insufficiency of circulation. Still it is emphasized by Warburg that in many cases the prognosis must be considered good, as many cases not giving conspicuous troubles pass unnoticed unless a detailed examination including electrocardiography is carried out every or every other day immediately after the accident.

Still it is necessary to ask: which criterions are wanted for the diagnosis: traumatic injury of the heart? First and foremost it should be maintained, that the cases in question must present some

or other decisive and substantial signs of an organic lesion of the heart i.e. unquestionable signs of cardiac insufficiency and/or pathognomonic symptoms recognized by stethoscopic, roentgenological or electrocardiographical examination. The importance of this is stressed in a following chapter of this paper.

Moreover it must be regarded as essential that these decisive symptoms are discernible shortly after the accident. Though an exact term can not be given, as some cases, e.g. some cases of coronary insufficiency, may be seen to develop rather slowly, it must be stated that signs of a heart trouble observed during the first days after the accident will make the traumatic etiology of the case more likely than symptoms which develop later. Significant is also, as already mentioned, the localization of the trauma to the precordium or its nearest surroundings and its strength, slight traumata being less apt to procure a lesion of the heart or the pericardium than heavier blows.

Some perplexity may arise, where persons suffering from the sequelae of *contusio thoracis* have had a heart-disease before the accident. In such cases the decision of the doctor and of the insurance-company is bound to be rather approxinative with regard to the possible influence of the accident and with a tendency to question the traumatic etiology of the disease. Often any compensation for damage must be denied, as the experienced aggravation is nothing but what should be expected to happen in any case.

Concluding one may say, that unquestionable signs of an organic lesion of the heart developing shortly after a heavy blow having damaged the chest-wall in the heart-region are the essential conditions for the recognition of traumatic injury to the heart.

## II. Arteriosclerotic patients suffering from sequelae *contusio thoracis* but presenting no signs of cardiac disease.

A typical case is presented by an elderly person who falls on something hard and hits his chest or gets his chest squeezed between solid things damaging the chest-wall but injuring neither lungs nor heart. It may be supposed that he has never before suffered from any internal disease of importance, though he may have presented some symptoms of arteriosclerosis and his blood-pressure may be

elevated. A person of this kind will usually be confined to bed for some time, as he may exhibit some signs of collapse or shock after the accident. Staying in bed he may develop a pneumonia or an attack of bronchitis, getting fever and losing his vitality; thus he is handicaped and easily tired out when he gets out of bed again. Oedematous swellings of the ankles may appear, and throughout the coming months he stalks around always tired and not able to resume his work, complaining of pains located to the bruised parts of the chest and of shortness of breath. But the medical examination will disclose besides arteriosclerosis, debility (especially muscular) and local sequelae contusionis of the chest-wall no evidence of organic lesions neither of the lungs or heart nor of the central nervous system. Contrary to the patients belonging to group III, i.e. the patients suffering from a traumatic neurosis, the arteriosclerotic patients will be lowspirited rather than neurotic, tired rather than agile.

In spite of the absence of distinct organic disturbances it is obvious that the accident has damaged and invalidated this person. It must be asked why it is so. What has really been happening to this patient after the accident? In many cases this question can not be answered fully. It may be a matter of minor thromboses, embolitions or embolies localized either to some dumb zone of the cerebrum or the myocardium not giving distinct but only diffuse symptoms. Therefore one is often forced to contend oneself with the thought that arteriosclerotic patients usually are less able than normal persons to tolerate even slight injuries and to endure being laid up in bed. This may partly be due to the fact that these elderly and arteriosclerotic patients when confined to bed for some time are rapidly losing the physical training which hitherto has kept them going, whereas they have not got the normal ability of resuming it when getting out of bed again.

Thus the accident has been harmful to the arteriosclerotic patient in a way different from what is met with in cases of traumatic lesions of the heart. The oedematous swellings of the ankles which are seen in arteriosclerotic and debile patients that have stayed in bed for some time are the signs of a local circulatory disturbance and not of a universal insufficiency of circulation. As a rule the thoracic pains have not got the character of an angina pectoris and are not located to the heart-region; they are clearly caused by the

damage done to the tissues of the chest-wall. The shortness of breath generally presenting itself as a working-dyspnoea may be due to the pronounced debility, to the lack of muscular strength which makes even slight exercises straining.

### III. Patients suffering from a traumatic neurosis which has taken the form of a cardiac and respiratory neurosis.

#### *Typical case. Description.*

This group includes the greatest number of patients suing the insurance-companies for damage supposed to be traumatic lesions of the heart. Typical is the vigorous and hitherto in all respects healthy man who has an accident, his thorax being squeezed between the steering-wheel and the back of the seat in a motor-car, or comes down with a heavy thing on top of him or is knocked down and bumped by an angry bull. He may be in a state of *shock* after the accident and be confined to bed for some time suffering from various bruises and perhaps feverish because of a pleurisy or a hemothorax — though without any distinct signs of a heart lesion. Getting out of bed in the convalescence he still feels weak. His health does not improve, on the contrary he seems to get worse. If he tries to resume his work he is forced to give it up again. He complains of pains in the chest or in the back, of palpitations, shortness of breath and of not being able to sleep well. Labouring under a *fear of traumatic heart-disease* menacing him with invalidism and economic difficulties to come, he impresses his surroundings as being in an excitable state of mind. He often does not understand his own situation very well and therefore for a time sways between optimism and hypochondria. Feeling this state of mind unendurable he resorts to a conviction of an organic lesion of the heart being the matter, in this way relieving himself of the insufferable feeling of uncertainty. For many patients this is less difficult than to maintain a belief in good chances for recovery in spite of the fact that pains, shortness of breath and palpitations are persisting. Thus, when the right moment comes, the patient sues the insurance-company for damage in order to get a financial aid — perhaps for the starting of a new way of living — and in order to get at the same time an official acknowledgement of the reality of his disease, making an end to any doubt which still might harass him or his surroundings, an acknowledgement serving the patient as a kind of *rehabilitation*.



*Clinical aspect. Survey.*

In many ways there is a dominating similiarity as regards the subjective and objective symptoms between such traumatic cases and the non-traumatic cases of cardiac and respiratory neurosis described by the author in a previous paper (Author: Cardiac and respiratory neurosis. Acta med. scand.: 99: 162, 1939). This may be gathered from the tabulations here presenting a survey of a series of 22 patients who during the years 1933—38 were sent to me from the insurance-companies for an examination of their cases. (In one for these cases (journ. no: 1429) the damage was due solely to a violent and most acute bodily exertion and not to any mechanical injury; this case is discussed here in order not to interrupt the series and because in some other respects this case is very similar to those others). In all 22 cases the insurance-companies were sued for damage owing to the doctor's conviction or assumption of the patient being a victim of a traumatic and organic lesion of the heart.

Of these 22 patients 20 were men and 2 were women. Their age varied from 33 to 60 years.

**Table 1.**

*The accidental happenings were reported as:*

Pl. No:

- 627 Tumbled down from a wagon on the top of a fence, hit the left side of his chest.
- 653 Fell down a staircase in a dark cellar his fall being checked as the the right side of his chest collided with an upright standing stick of iron.
- 673 Fell while cycling on account of the breaking of the cycle's forepart, his right shoulder and the right part of his chest hitting the pavement.
- 712 Fell from wagon, twisted his left foot, got a wound in his left calf and slammed the left side of his chest against the earth.
- 762 Lost his balance on slippery ground, fell and knocked his left knee and the left side of his chest against a wooden box.
- 937 Was knocked about by an angry cow and squeezed against a stone-wall, bruised the left side of his chest.
- 994 Fell and hit the front of her chest on a slippery floor.
- 1139 Lost balance while walking and fell, the front of his chest hitting the wooden floor.
- 1208 Lost balance on slippery ground, fell down on his back.

- 1283 Collided with a motor-car while cycling, was hit by the fender of the car and whirled to the ground damaging various parts of his chest.
- 1429 Under the transport of a grand piano which threatened to slide away he was forced to put all his strength into a momentary stabilizing effort. Soon after that he got sick with shortness of breath, a feeling of oppression followed by a mortal fright and, a little later, by stabbing pains in the heart-region.
- 1432 Fell while cycling and knocked the front of his chest against the hand-bar of his cycle.
- 1505 Slipped on cycle, came down and hit front of her chest against the cycle's hand-bar and the ground.
- 1546 Was bumped by an angry bull, taken on the horns, knocked down and squeezed between the front of the bulls head and the ground, damaged large parts of his chest.
- 1767 Lost balance while walking, came down, the left side of his chest hitting the pole of a horse-wagon.
- 1829 Fell from a truck and hit the left side of his chest on stone-pier.
- 1834 Got his chest squeezed between side of a ship and some heavy machinery.
- 2050 In a motor-accident he got his chest compressed between steering-wheel and back of the seat.
- 2152 Fell on slippery ground and hit side of his head and left side of his chest.
- 2167 Stumbled and came down hard with right side of his chest on an iron rail.
- 2184 Fell down a staircase hitting left side of his chest on the edge of the steps.
- 2307 Was knocked down by a horse-waggon one of its wheels going over left side of his chest.

Table 2.

*Immediate sequelae contusionis were:*

Fractura costarum .....	12 cases
of these fractura complicata .....	1 case
Infractio costarum .....	3 cases
Marked condition of shock .....	3 cases

Table 3.

*Complications were:*

Laesio pulmonis c. hemoptysis .....	5 cases
of these: hemoptysis permagn.....	2 cases
hematothorax + pneumonia .....	1 case
hematothorax + emphysema subcutanea..	1 case
hemato-pneumothorax .....	1 case

Bronchopneumonia .....	1 case
Pleurisy .....	1 case
Bronchitis acuta in bronchitis chron. ....	2 cases

Table 4.

*Subjective and objective symptoms developing in the period of time between the accident and my examination of the cases.*

Anxiousness of mild degree .....	16	cases
Marked fear .....	4	»
Cough .....	6	»
Working-dyspnoea .....	19	»
Paroxysmic shortness of breath during rest .....	9	»
Palpitations .....	15	»
Extrasystolia .....	2	»
Pains in the chest located to the bruised parts ..	18	»
» » » » » » » precordium.....	9	»
» located to the back .....	8	»
Palpable changes of muscles combined with soreness and pains:		
located to the bruised parts .....	15	»
» » » precordium .....	9	»
» » » back .....	7	»
Feeling of oppression .....	15	»
Symptoms of a dysfunction of the thyroid gland	0	»
Nykturia .....	0	»
Proteinuria .....	0	»
Oedematous swellings of the ankles .....	1 (?)	»
Stasis pulmonum.....	1 (?)	»
» hepatis .....	0	»
Arytmia cordis (extrasystolia excepted) .....	0	»
Stethoscopical signs of an organic heart-failure ..	0	»
Electrocardiography:		
left-preponderance .....	8	»
right » .....	1	» <sup>1</sup>
other changes.....	0	»
Roentgenological changes:		
emphysema pulmonum bilateralis .....	17	»
» » unilateralis .....	2	»
cor pendulum.....	1	» <sup>2</sup>
other changes.....	0	»

<sup>1</sup> in a patient who had suffered from a right-sided hemato-pneumothorax and now presented a retraction of the right side of the chest, a scoliosis and a left-sided vicarious emphysema of the lung.

<sup>2</sup> in a slender, asthenic patient presenting a hyperrelaxed kypho-lordotic posture.

Decisive changes of blood-pressure .....	0	cases
Reaction to test of heart-function indicating insufficiency of circulation.....	3 (?)	" "
Reaction to test of heart-function indicating neurosis	4	" "
Secondary neuritis radicularis .....	3	" "

### *Symptoms and explanation.*

The symptoms most often complained of were anxiousness, pains in the chest or in the back, shortness of breath, a feeling of oppression and palpitations. These signs of discomfort were usually accentuated when the patients were making an attempt to resume work.

### *Pains.*

Generally the pains had not got the character of angina pectoris as they were not located to the precordium but to other parts of the chest or to the back, and they were slighter and more like soreness or stinging sensations; besides they were usually of shorter duration than angina pectoris and much less alarming.

These pains were partly caused by the bruised muscles and periostium of the ribs, and partly they were caused by functional changes in the muscles overstrained by statical work conditioned by *anomalies of posture*. In many patients, the anomaly of posture had been habitual for years preceding the accident. the signifi-

<sup>2</sup> Conspicuous and synchronous acceleration of breath and pulse during 20 rapid and extreme flexions on the knees besides retarded returning to rest-values. In 15 out of these 22 cases the reaction to this test was in no way different from the normal. In 3 cases (Journ. no: 1208, 1429 and 1767) the acceleration of breath and pulse seemed to be on the verge of anomaly. The rest, 4 cases are discussed next.

<sup>4</sup> An abnormal reaction was observed in 4 cases presenting theatrically shortness of breath but no corresponding acceleration of pulse at the very beginning of the test followed by a slowing down again to more peaceful conditions even before the exercises were finished.

<sup>5</sup> The diagnosis: «secondary neuritis radicularis» was based upon alterations of sensibility and/or paraesthetic sensations in the arm or hand i.e. in the region whose innervation corresponded with the innervation of either the damaged parts or the altered static muscles in the chest-wall.

(Ad table 5, p. 62—63.)

<sup>1</sup> Anomalies of posture: explanation of abbreviations:

Dk = increased dorsal kyphosis, Fb = flat-back, Huc = hyperextension of hip-joints, Ll = increased lumbar lordosis, O = obesity-posture, Pa = hyper-relaxed, asthenic posture, Ps = soldier-posture, S = scoliosis, Tba = barrel-shaped and distended thorax.

<sup>2</sup> present even before the accident according to anamnestic information.

<sup>3</sup> This case was due to no mechanical injury but merely to a violent and acute physical exertion.

<sup>4</sup> present even before the accident according to anamnestic informations.

Table 5. Survey

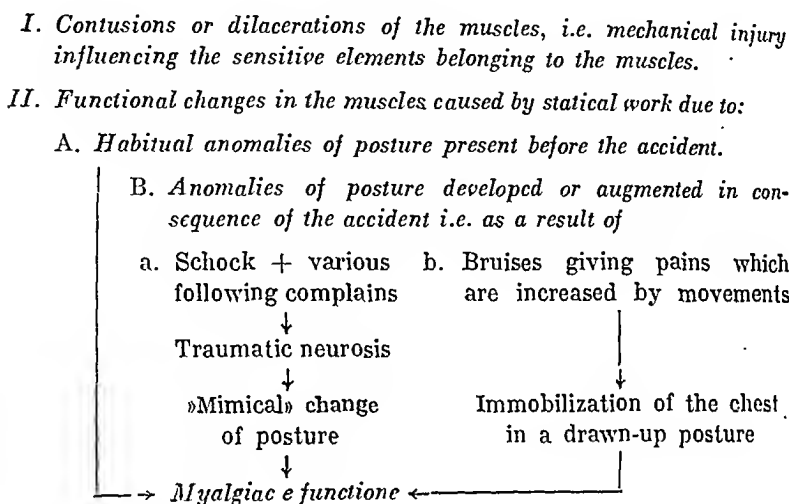
Journ. No:	Sex	Age: years	State of nutrition	Anomalies of posture <sup>1</sup>	Effect of trauma	Complications	Duration of confinement to bed: years	Length of time between accident and examination of case: years
627	♂	56	m	Ps, Tba	fract. cost. V—VI sin.	÷	1/12	7/12
653	♂	34	m	÷	cont. thoracis	÷	1/12	3/12
673	♂	33	m	Pa, Ll, Dk	cont. thoracis	÷	1/12	2/12
712	♂	62	m	Ps, Tba	cont. thoracis	÷	1/12	8/12
762	♂	51	m	Pa, Ll, Dk	cont. thoracis	÷	6/52	9/12
937	♂	36	m	÷	cont. thoracis	÷	2/52	1
994	♀	59	m	Ps, Dk (juv-nilis)	fract. cost.	laesio pulmonis, hæmoptysis	2/52	9/12
1139	♂	45	m	÷	cont. thoracis	÷	?	1
1208	♂	59	>m	(O), Ll, Dk	cont. thoracis	÷	1/12	3/12
1283	♂	47	m	Ll, Dk	fract. cost.	÷	2/12	1
1429 <sup>3</sup>	♂	38	>m	(O), Ps	myalgiae funct. ac. thorac. et dorsi	laesio myocardi ac.?	1/12	5/12
1432	♂	60	m	Ps, Tba	cont. thorac.	bronchitis febrilis	4/365	2/12
1505	♀	41	>m	O, Ll, Tba	fract. cost. IV, V, VI sin.	laesio pulm., hæmoptysis	3/12	11/12
1546	♂	56	m	Hac, Dk	fract. cost.	÷	1/12	5/12
1767	♂	54	>m	O, Ps, Tba	fract. cost. V sin.	influenza	3/52	7/12
1829	♂	50	>m	(O), Fb, Dk, (Tba)	fract. cost.	laesio pulm., hæmatothorax, pneumonia	6/52	6/12
1834	♂	51	>m	(O), Ll, Dk	fract. cost.	bronchopneumonia		8/12
2050	♂	40	m	Dk (juvenilis), S	fract. cost.	hæmato-pneumothorax dxt.	3/12	1½
2152	♂	54	>m	(O), Ll, Dk, Tba	fract. cost.	bronchit. acuta in chronica	3/52	5/12
2167	♂	48	>m	O, Ll, Dk, Tba	fract. cost. VII, VIII, IX, X, XI, XII dxt., cont. renis dxt.	hæmato-pneumothorax dxt., emph. subcut., hæmaturia pleurit. sin.	3/52	2
2184	♂	36	m	Pa, Hac, Fb, Dk	cont. thor.		3/12	9/12
2307	♂	53	m	Hac, Fb, Dk	fract. cost.	÷	5/52	1

Anxiousness	Cough	Working-dyspnoea	Paroxysmic shortness of breath	Palpitations	Extrasystolia	Pain in bruised parts of chest	Pain in precordium	Pain in back	Feeling of oppression	Oedematous swellings	Stasis pulmonum	Other stethoscopic anomalies	Reaction to test of heart-function indicating insufficiency of circulation	Reaction to test of heart-function indicating neurosis	Peculiarities in ECG	Röntgenological observations (E. p. = emphys. pulm.)	Blood-pressure measured by oscillogometer	Signs of secondary neuritis radie.	Palpable changes of muscles in bruised parts of chest	Palp. changes of muscles in precord.	Palpable changes of muscles in back	
(+)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	left-prepond.	E.p. bilat.	145/65	+	+	+	+	
(+)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	130/65	+	+	+	+	
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	cor pendulum	120/60	+	+	+	+	
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	E.p. bilat.	E.p. bilat.	145/80	+	+	+	+
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	E.p. bilat.	E.p. bilat.	150/70	+	+	+	+
(+)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	120/50	+	+	+	+	
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	E.p. bilat.	E.p. bilat.	120/70	+	+	+	+
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	140/60	+	+	+	+	
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	E.p. bilat.	E.p. bilat.	150/65	+	+	+	+
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	E.p. bilat.	E.p. bilat.	140/65	+	+	+	+
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	E.p. bilat.	E.p. bilat.	120/80	+	+	+	+
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	left-prepond.	E.p. bilat.	150/70	+	+	+	+	
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	E.p. bilat.	E.p. bilat.	140/70	+	+	+	+
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	left-prepond.	E.p. bilat.	160/60	+	+	+	+	
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	left-prepond.	E.p. bilat.	140/70	+	+	+	+	
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	left-prepond.	E.p. bilat.	145/70	+	+	+	+	
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	left-prepond.	E.p. bilat.	140/70	+	+	+	+	
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	left-prepond.	E.p. bilat.	120/70	+	+	+	+	
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	right-prepond.	E.p. sin.	160/80	+	+	+	+	
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	E.p. bilat.	E.p. bilat.	130/60	+	+	+	+
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	left-prepond.	E.p. sin.	110/60	+	+	+	+	
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	left-prepond.	E.p. bilat.	125/60	+	+	+	+	

Notes ad table 5 see p. 61.)

cance of this point is discussed in a following chapter. In other patients it developed on account of the accident. Thus in accordance with the results of the author's previous investigations the causes of the muscular pains in these patients may schematically be recognized as follows:

Table 6.



This means that pains caused by contusions may cooperate with traumatic neurosis in provoking a development of or an augmentation of *postural anomalies* and of *emphysema*. The fact that *dilation of the lungs and postural anomalies were observed in 19 out of 22 cases* settles the matter and emphasizes the similarity between these cases of traumatic neurosis and cases of non-trauma-

Table 7.

(The figurs indicate the number of patients.)

	Total	Pains from bruised parts	Myalgiae e functione located to	
			precordium	back
Constant and bilateral emphysema of the lungs	17	14	8	7
Constant but unilateral emphysema of the lungs	2	1	1	1
No constant emphysema of the lungs .....	3	3	0	0

tic cardiac and respiratory neurosis. The very same factors: muscular pains, postural changes, development of emphysema and neurotic disturbances are cooperating in neurotic cases of both categories forming vicious circles, every single factor influencing the other factors.

### *Shortness of breath.*

The shortness of breath met with in the cases of traumatic neurosis is caused by *neurotic and emphysematous changes in the mechanism of respiration*. The character of the dyspnoea varies individually, but generally it is very unlike the quiet, regular, at the beginning and at the end of exercise gradually augmenting resp. gradually decreasing dyspnoea, which is seen in patients suffering from an insufficiency of circulation. In these cases of traumatic neurosis, precisely as in cases of non-traumatic cardiac and respiratory neurosis, the shortness of breath comes and goes in a markedly abrupt manner (*neurotic pseudo-dyspnoea*) and is clearly connected with *psychic alterations*; this may be experienced e.g. during the phases of a medical examination. Though a shortness of breath may be observed during exercise the resting-dyspnoea is often more pronounced. A paradoxical reaction to tests of heart-function presented by some of these patients is discussed above (note<sup>4</sup> to table 4). Conspicuous is often the *missing parallelism between the rate of pulse and the rate of respiration* when e.g. suddenly and without physical provocation the patient dramatically starts a stertorous breathing while his pulse continues nearly unaltered in rate and rhythm. The type of respiration is often the «neurotic» described in the authors previous publications with sporadic, forced inspirations followed by a retarded returning to the habitual level. All this points to the nervous origin of the shortness of breath in the patients discussed here. Such dyspnoea is not caused by an insufficiency of circulation but by a *respiratory neurosis*. Besides it is distinctly seen in most of these patients that the respiration is of mixed abdominal-thoracic or purely thoracic type. Thus all of the three phenomena constituting together the conditional and pathognomonic *triade of the pulmonary emphysema*: the altered type of respiration, the postural anomaly and the dilated lungs are observed in these



patients precisely as in patients suffering from a non-traumatic neurosis. The pulmonary emphysema is an integrant factor in the patho-physiology of such cases and cooperates with the nervous excitement in vicious circle responsible for the shortness of breath. One might say that the working-dyspnoea complained of by these patients is due to the emphysema of the lungs whilst the paroxysmic shortness of breath during rest is of nervous origin, but then the fact is that neurosis and emphysema are mutually influencing each other, an enlargement of the emphysema tending to aggravate the nervous disturbances and vice versa.

### *Palpitations.*

In many cases the heart-rate and the occurrence of palpitations are obviously *dependent upon psychic fluctuations* in the same manner as is the shortness of breath. An independence of exercise, e. g. the pulse-rate slowing down under gymnastic exercises which for the time being occupies the mind of the patient, may be very conspicuous. Such changes are clearly due not to an organic heart-failure but to nervous disturbances.

40904

### *Anomalies of posture.*

The postural anomalies repeatedly mentioned above were seen in all but three cases (journ. no: 653, 937 and 1139) i.e. the only cases not presenting any emphysema of the lungs (v. table 5). As a detailed description of these anomalies of posture is given in previous papers (Author: Emphysema of the lungs etc. Copenhagen, Munksgaard. 1942) it will suffice here to refer to tabel 5 (column 5 and note<sup>1</sup>). The decisive importance of such static changes with regard to the straining of the muscles in the chest-wall and in the back and with regard to the development of pulmonary emphysema is mentioned repeatedly above and has been delt with more thoroughly previously.

It must be mentioned that most of these patients suffering from *sequelae contusionis thoracis* undoubtedly had suffered from postural anomalies even before the accident. The static changes were too pronounced and too fixed to be of recent date, and in most cases their existence throughout many years, even decades,

in advance of the accident would be confirmed by the patients. The frequent occurrence of such cases (at least 16 out the total 22) suggests in itself that these postural anomalies can partly be made responsible for the development of the illness constituting a *disposing factor*, as naturally the static changes involved by neurosis or pains will develop to a higher degree in patients already displaying a postural anomaly of similar kind than in hitherto normal individuals. As to the muscular complaints, it is but natural that muscles strained in advance through abnormal static exertions are sooner overstrained by extra statical work than normally functioning muscles. Finally, it may be mentioned that generally the tendency to shortness of breath, to palpitations and to a feeling of oppression corresponds to the degree of the postural anomalies and the distension of the lungs.

#### *Examination of heart and lungs. Results.*

As stated in table 4 and 5 the detailed examination of heart and circulation gave a negative result in practically all cases.

In a few cases the repeatedly and oscillometrically measured systolic blood-pressure was slightly raised and varied but little under exercises, whereas in some other cases the diastolic blood-pressure was rather low. Still these variations were insignificant and not pervading.

In some of the patients a certain tendency to *cutaneous vasomotor lability* and fits of flushing combined with a moderate and unstable tremor indicated the possibility of a hyperfunction of the thyroid gland. But no other symptoms of this and especially no metabolic disturbances were observed.

The stethoscopical and roentgenological examination of the patients disclosed in the majority of cases besides the existence of emphysema nothing particular. The electrocardiograms betrayed no definite myocardiac anomalies (v. table 4 and 5).

More complicated tests of heart-function such as electrocardiography under exercise or under experimentally anoxaemia were not performed. A much simpler test was applied (v. Table 4 and note<sup>3</sup> and <sup>4</sup>) and showed useful making obvious in some cases the neurotic origin of the dyspnoea, which for that reason will be

better described as a *neurotic pseudo-dyspnoea*. Reactions to this test clearly indicating an insufficiency of circulation were not seen, though in three cases (journ. no: 1208, 1429 and 1767.) the result seemed doubtful. The neurotic pseudo-dyspnoea may be observed in patients presenting no or very small changes of heart-rate, whereas in other patients the heart-rate is found much accelerated, even permanently accelerated, before, during and after physical exercise, without any dyspnoea at all. Such individual variations may be said to be significant for the type of the neurotic case in question: whether predominant respiratory or cardiac.

In cases, where no special complications such as pleurisy or haematothorax were seen, the examination of the lungs and mechanism of respiration disclosed nothing but the phenomena mentioned above, which are the pathognomonic signs of pulmonary emphysema, i.e. the changed type of respiration, the postural anomalies and the distension of the lungs. In addition one might of course find are increased residual capacity and a decreased vital capacity. X-ray-examination disclosed the usual signs of a thoracic and pulmonary enlargement.

### *Diagnoses. Epicrisis.*

As a result of the problems here discussed the diagnoses of the cases must be as stated in table 6. Although the accidents might very well in a great part of the cases have resulted in a mechanical injuring of the heart as the blows were heavy and directed against the precordium, and although in some cases the complaints seemed earnest immediately after the accident, it must be maintained that in none of all cases any substantial and decisive symptoms of an organic heart-lesion were observed; only in three cases the result of the examination gave a vague indication of a disease of that kind possibly being the matter. In one case (journ. no: 1429) an acute myocardiac lesion due to an acute physical exertion was likely but had left no objective signs at all. In two more cases (journ. no: 1208 and 1767) the applied, simple test of heart-function gave a questionable result, no other symptoms of an organic heart-failure being observable.

Table 8.

Patient no:	Diagnoses:
627	Cont. thorac. seq., fract. cost. seq., emphy. pulm., periostit. costar., myalgiae intercostal., neurosis cordis et respir. posttraumat.
653	Cont. thorac. seq., myalgiae intercostal., neurosis cordis et respir. posttraumat.
673	Cont. thorac. seq., emphy. pulm., myalgiae intercostal. et dorsi.
712	Cont. thorac. seq., emphy. pulm., myalgiae intercostal. et praecordii, neurosis cordis et respir. posttraumat.
762	Cont. thorac. seq., emphy. pulm., myalgiae intercostal. region. axill sin. et praecordii, neurosis cordis et respir. posttraumat.
937	Cont. thorac. seq., periostit. costar., myalgiae intercostal., hypochondria.
994	Cont. thorac. seq., kyphosis dors. (juvenilis?), emphy. pulm., myalgiae variae thoracis, neurosis cordis et respir. posttraumat.
1139	Cont. thorac. seq., neurosis cordis et respir. posttraumat.
1208	Cont. thorac. seq., adipositas, emphy. pulm., myalgiae thorac. et dorsi, neurosis cordis et respir. posttraumat., <i>laesio myocardii?</i>
1283	Cont. thorac. seq., emphy. pulm., myalgiae thorac. et dorsi, neurosis cordis et respir. posttraumat.
1429	Adipositas, emphy. pulm., <i>laesio myocardii?</i> (e funct. ac.), myalgiae thorac. et dorsi, neurosis cordis et respir. posttraumat.
1432	Cont. thorac. seq., emphy. pulm., catarrh. chron., bronchit. ac. in chron., neurosis cordis et respir. posttraumat.
1505	Fract. cost. seq., adipositas, emphy. pulm., myalgiae thorac. et dorsi, neurosis cordis et respir. posttraumat.
1546	Fract. cost. seq., emphy. pulm., neurosis cordis et respir. posttraumat.
1767	Fract. cost. seq., adipositas, emphy. pulm., myalgiae thorac. et dorsi, neurosis cordis et respir. posttraumat., <i>laesio myocardii?</i>
1829	Fract. cost. seq., emphy. pulm., myalgiae thorac. et dorsi, neurosis traumatica.
1834	Fract. cost. seq., adipositas levi gr., emphy. pulm., myalgiae thorac. variae, neurosis cordis et respir. posttraumat.
2050	Fract. cost. seq., haematothorax dxt. seq., emphy. pulm. unilat. sin., neurosis cordis et respir. posttraumat.
2152	Fract. cost. seq., adipositas, emphy. pulm., myalgiae thorac. variae, bronchit. recidiva.
2167	Fract. cost. seq., adipositas, haematothorax dxt. seq., emphy. subcut. thorac., contus. renis, emphy. pulm. unilat. sin., myalgiae thorac. et dorsi.
2184	Cont. thorac. seq., emphy. pulm., myalgiae thorac., neurosis cordis et respir. posttraumat.
2307	Fract. cost. seq., emphy. pulm., myalgiae thorac. variae, neurosis evi gr. traumat.

Nevertheless it is generally experienced that the symptoms present in such cases as those here discussed, as well as in cases of non-traumatic cardiac and respiratory neurosis, will convince the doctors in charge that an organic heart-failure is the matter, especially in cases where the nervous stigmata are relatively well controlled by the patients, although the detailed examination only discloses the signs of a cardiac and respiratory neurosis. Under such circumstances it seems necessary to emphasize that the *discrimination between merely functional and organic heart trouble must be based upon the absence or the presence of substantial symptoms absolutely pathognomonic for an organic heart-lesion*, as pains in the chest, shortness of breath, palpitations and tachycardia without such substantial symptoms are ambiguous and insignificant, these complaints being often experienced in purely functional cases.

One might ask: may we not come across patients who, suffering from an organic heart-lesion, at least for some time do not present such substantial symptoms as are here considered conditional for the recognition of the disease? To this the answer must be, that according to common experiences regarding heart-diseases such patients are encountered relatively seldom. As this nevertheless, points to the existence of a risk for misjudgment it is important that this risk be limited by detailed and often repeated examinations during the time immediately following the accident. When this is properly done, the chances are that exceptionally few cases of organic heart-lesion will be ignored, very few cases in comparison with the big number of purely functional cases met with.

In addition it would be natural to ask, if the recognition of a case of cardiac and respiratory neurosis as a case of organic heart-lesion and the dispositions, e.g. the payment to the patient of a compensation for damage, made on account of that, would have serious consequences?

For the insurance-companies this would mean an increase of the payments, though not of greater financial importance; so this point would be rather insignificant. The consideration for the patient himself and his future constitutes the main point, as the purpose of the doctor and the insurance-company is to help the patient to regain his health, his capacity for work and his resumption of all normal functions as well and as early as possible.

This is the *essentiel* point, as it may without doubt be *disastrous for a person to be unjustly recognized as suffering from an organic heart-failure* even if this involves a pecuniary compensation. If a thing like that happens to a neurotic patient his recovering is apt to be retarded and his confidence in himself is hampered proportionate to the limitation of what he is encouraged or rather allowed to perform.

It may be added, that in uncertain cases the very best chance for the patient lies in the doctor sustaining the patients optimism by confirming his belief in recovery and in his ability of resuming a normal life.

Therefore, the answer to the question raised above is affirmative; the consequences might very well be serious. This is the reason why it should not be wise to drop clauses which may protect the patients, who are suffering from merely functional troubles, from being recognized as having an organic heart-failure; therefore it must be regarded as *an unjustifiable fault of the doctor's to accept the diagnosis of an organic disease of the heart if substantial, pathognomonic symptoms are wanting*. Acting in accordance with these principles and suspending the final decision until the end of a reasonably long period of observation, one might happen to misjudge, at least for the time being, a few cases of organic heart-trouble, and surely this would be wrong, but it would concern in all very few cases and might, in most of these, do little harm. On the contrary, acting upon the unsound principle that in uncertain cases one should not dare to deny the patient the possibility of an organic heart-failure and of a compensation for damage, one unquestionably should do much more harm, as patients of that kind are in majority.

#### *Treatment.*

It may finally be mentioned that a mobilizing treatment of patients suffering from sequelae contusionis thoracis by means of *medical gymnastics* instituted soon after the accidents may add considerably to prevent the immobilization of the chest and the postural anomaly eliminating at the same time the tendency to persisting, functional disturbances. The point is to *effect a muscular relaxation* as soon as possible. In cases where there are no special complications such mobilizing procedures may be started within few days after the accident.

## Summary.

A series of patients suffering from the sequelae of thoracic contusions is presented. In most of these cases the complaints were not caused by any organic heart-lesions but by the bruises inflicted on the chest-wall and by a traumatic cardiac and respiratory neurosis. The symptoms of this traumatic neurosis were very much like the symptoms of the non-traumatic cardiac and respiratory neurosis. Conspicuous subjective symptoms were dyspnoea, either working-dyspnoea or paroxysmal shortness of breath during rest, a feeling of oppression, palpitations, pains in the chest or in the back besides anxiousness and in some cases pronounced hypochondria or a real anguish. Its distinguishing objective symptoms were first and foremost those which together form the triad pathognomonic for the pulmonary emphysema: a) the respiration altered from abdominal to mixed or purely thoracic type, b) the changed posture, i.e. postural anomalies and c) the dilation of thoracic cavity and lungs. In addition some patients presented the special neurotic type of respiration recognized by sporadic, forced inspirations followed by retarded return to habitual level. Some presented a mutual independence of rate of pulse and respiration, both being influenced decidedly more by psychic alterations than by physical exercise, so that paradoxical reactions to tests of heart function could be seen, quite unlike the reactions of patients suffering from organic heart failure. Most of the patients presented local, palpable alterations of density in the static muscles of the chest-wall and the back: myoses e functione. The combination of these symptoms accounts sufficiently for the complaints. As the majority of these patients had displayed habitual anomalies of posture even before the accident, it is likely that these anomalies of posture have contributed to the development of the disease.

It is important that cases of cardiac and respiratory neurosis, traumatic or non-traumatic, will not be misinterpreted and considered cases of organic heart-failure, as this may lead to a lasting invalidation of the patients. The principle of not recognizing a case as one of organic heart-disease if substantial and pathognomonic symptoms are missing eliminates this unfortunate possibility.

A mobilizing treatment by means of medical gymnastics started within few days after the accident is recommended.

---

From the Medical (Prof. Svartz) and Pathological Department (Prof. Henschen) of the Karoline Hospital, Stockholm.

## Spleen and liver abscesses due to Friedländer's bacillus.

By

BERTIL SWEDIN and ÅKE LILJESTRAND.

(Submitted for publication October 23, 1944).

---

Friedländer's bacillus is a relatively rare cause of liver abscesses. Thus Boettiger, Weinstein and Werne, who described two cases of their own, found only some 25 cases in the literature. The course of the disease is a rule septic, with enlargement of the liver, abdominal pains and usually icterus, terminating in death rather rapidly or after the lapse of several weeks. In some of the cases renal abscesses, in addition to the multiple liver abscesses, were found on dissection. A more protracted case — which, unfortunately was not subjected to post-mortem examination, — was reported by Carnot, Dumont and Libert. It was that of a woman aged 44, who for more than a year had shown the above-mentioned symptoms in four periods before her death during the final stage. Cultures from the patient's blood and bile yielded, on several occasions, a growth of Friedländer's bacillus. — The same authors obtained a positive Friedländer culture from bile withdrawn with a duodenal sound from another patient, whose disease took the form of a non-complicated hepatitis, with complete recovery after seven weeks.

The usual view, according to which Friedländer's bacillus is localized mainly to the respiratory tract and induces infection there, is considered by Baehr, Shwartzman and Greenspan to be erroneous. Out of 198 cases where they found Friedländer's bacil-



lus, the location was abdominal in 163; in 61 cases it was observed on perforation of the appendix or colon, in 50 it was found in the urinary organs and in 46 in the gall ducts. It should be noted, however, that in a strikingly large number of the reported cases of liver abscess the patients had suffered from chronic bronchitis. In one of these cases Friedländer's bacillus was cultivated from a bronchiectasis (Hegler and Nathan). The said authors also found that such abscesses were of a peculiar type, with a very marked necrotic element.

In view of the rarity of these cases, none of which has previously been reported in Scandinavia, we consider ourselves warranted in publishing the following case: —

Hospital record No. 2519/43, relating to the case of a woman aged 60, without hereditary taint. Partus 1908 and 1910 without complications. She had had the usual diseases of childhood. Among other previous diseases, mention may be made of Graves' disease, for which she was operated in 1914. In 1920 she underwent a cure for a hemorrhagic gastric ulcer. Six years after the menopause, which occurred at the age of 46, she suffered from uterine hemorrhages, which, however, ceased after abrasion.

The disease in question set in during a temporary visit to Stockholm. On the 29th November 1942 she suddenly fell ill, with shivering, fever, cold in the head and sore throat. Her temperature kept between 38° and 39° centigrade. A day or two afterwards she had great difficulty in swallowing, fluid food coming out through her nose when she tried to eat. On the 3rd December she was sent to a hospital for infectious diseases under the diagnosis of diphtheria (?) and the following entry was made in the hospital records: «General condition good, no paresia peripherally, speech not particularly nasal». A specialist's report, dated 4th December, ran as follows: «Small tonsils. Intense reddening and swelling in the posterior palatal arches, especially on the left side, where an infiltration, involving also the posterior wall, can be palpated. On intonation, the soft palate practically does not move at all (Whether this is due to an infiltrate or to paresia cannot be determined)». Laboratory tests: Schick's reaction negative. A direct preparation from the throat contained no diphtheria bacilli. Urine: Almén's test positive. Blood sugar 180 mg %. Blood, see the Table on p. 77. — The throat trouble diminished from day to day. As she was evidently not suffering from diphtheria, she was transferred on the 6th December 1942 to the medical department of the Karoline Hospital, under the diagnosis diabetes mellitus and granulocytopenia.

Her general condition, on admission to the hospital, was unaffected. No signs of cardiac incompetency. Ample flesh and rather weak muscles. Pale colour of the skin. On the anterior side of the left thigh there is intensely painful swelling, as large as the palm of the hand, somewhat warmer than the environment. — Throat: the posterior palatal arches swollen

and somewhat reddened. On the left side the posterior palatal arch bulges out somewhat. The soft palate and the uvula move on intonation. The tonsils slightly reddened. — Lymph glands not palpable on the surface, except one as large as a shell almond behind the left maxillary angle. The thyroid gland not enlarged. Pulmones: nothing pathological on physical examination or x-ray irradiation. Cor: a rather soft systolic murmur, with the maximum over the apex. Roentgen examination showed a slight enlargement of the heart of the prone myocarditis type. Blood pressure 160/80. Abdomen: large and flaccid. Spleen and liver not palpable. Reflexes: the patellar, achilles and pupillary reflexes showed nothing abnormal. Babinski's sign absent. — Laboratory tests: blood (cells, see Table p. 77), sedimentation rate 114 mm/hour, coagulation and bleeding times normal, Hess' test negative, blood sugar 174 mg %. Blood culture: no growth. Urine: Heller's test positive, sediment: 10—15 white, a few red cells and one hyaline cast per field of vision. Almén's test positive, Benedict's test 1.4 %. Legal's test negative. Feces nothing pathological. — Sternal punctures were made on the 6th and 14th December 1942: »The preparations in both cases are similar. Marrow relatively rich in cells. Extremely serious lesions of myelopoiesis and reticulum. In the myelopoiesis left displacement and block in the ripening process after the myelocytes. Marked toxic and degenerative changes. Erythropoiesis: nothing abnormal. The reticulum markedly hyperplastic with increase of plasma cells and lymphoid types. Diagnosis: granulocytopenia in the marrow.» (N. G. Nordensson).

The 10th December: the patient seems rather apathetic and somewhat affected in general condition. The throat less reddened. She no longer complains of difficulty in swallowing. On the 13th December a fluctuation in the swelling on the left thigh was observed. An incision was made and a tube was inserted. The pus-cells consist as to 75 per cent. of polynuclear cells. Culture: abundant growth of  $\beta$ -hemolyzing streptococci.

In order to accelerate the healing, the patient was subjected to x-ray treatment on the leg. On the 21st December it was found necessary to make new incisions in the thigh. The abscess at first improved, but on the 7th January 1943 erysipelas appeared in the foot. It spread up the leg. Moreover, the abscess, in spite of very wide drainage, spread to the medial side of the thigh. The patient was then nursed, from the 8th to the 15th January, at the surgical department. The treatment there was sulphathiazole  $\frac{1}{2}$  g  $\times$  5. Moreover, since her admission to the hospital she had been treated with diabetic diet and insulin, so that the urine was kept almost free from sugar. From the 9th December to the 7th January she was given 150 g fresh bone-marrow per day. From the 6th December to the 7th January she received altogether 30 ml Heptomin, a solution of the antipernicious principle of the liver, besides repeated transfusions of 450 ml heparin blood from donors.

Her erysipelas had subsided and the sores were almost healed, when she was transferred to the medical department. On the 26th February 1943 she was discharged, after which she attended the medical outpatient department for diabetes control. Insulin treatment was suspended on the 4th

April 1943. The patient then returned to her home at Karlskrona, where she was kept under constant medical supervision. Her blood was throughout bad, and the only effect of a series of liver-preparation injections was that the blood kept at the same low level.

At the end of November 1943 she returned to Stockholm. After a few days she fell ill with great fatigue, subfebrile temperature and severe subjective cystitis trouble. The urine was very cloudy and malodorous, but never bloody. For this complaint she was nursed at the surgical department from the 13th to the 20th December 1943. Cystoscopy showed that the mucous membrane was almost everywhere reddened. The intravenous pyelogram was normal. Urine: Traces of albumin. Sediment: a few red, 10—12 white corpuscles per field of vision, masses of gram-negative rods. Almén's test positive, Benedict's test 0.5 %. Legal's test negative. — Blood sugar 216 mg per cent. She was treated with insulin, Pyelol per os and rinsings of the bladder, whereupon the bladder complaint rapidly disappeared.

As she still complained of great fatigue and as her blood values were low, she was nursed at the medical department from the 28th December 1943 to the 21st January 1944. Extract from the status 28th December: General condition unaffected, complains of great fatigue and looks very tired. No symptoms of cardiac incompetency. The flesh now somewhat reduced and flaccid. The operation wounds well healed. The throat pallid. Superficial lymph-glands: nothing pathological. Cor as before. Blood pressure 130/65. Pulmones, abdomen, reflexes: nothing noteworthy. — Sternal puncture on the 29th December: «Preparation rich in cells. Normal structure completely obliterated. The picture is dominated by markedly immature cells, and the character of the reticulum here and there is differentiated into myeloblasts. Nucleated red cells are practically absent. No megakaryocytes. The reticulum markedly hyperplastic, but without any increase of the plasma cells. Diagnosis: reticulosis with some differentiation into myeloblast leukemia.» (N. G. Nordensson).

The patient lay throughout with a subfebrile temperature. She received three blood transfusions. Was discharged, with improved blood values, for continued nursing at home. The urine then still contained masses of bacteria and a moderate number of white cells.

At the beginning of February 1944 the patient again fell ill. She had a cold in the head, a cough and a temperature of 38° C. After a week, during which she had partly lain in bed, she felt recovered. — On the 11th February, however, she suddenly fell ill again, with shivering and fever up to 40°, during which she was delirious. She had no trouble from the urinary ducts or respiratory organs. Sulphathiazole was administered on the 13th February, pneumonia being suspected. On the 14th February she was admitted to the medical department of the hospital. Her general condition on admission was greatly affected. Pale yellow complexion. Slight cyanosis of the lips. No edema or dyspnea during rest. No acetone smell in the exhaled air. Is so exhausted that she can scarcely speak. Otherwise nothing pathological at the physical examination. Blood pressure 95/50. Temperature 37.1°, pulse 80. The urine contained traces of albumin and

1.23 % reducing substance. In the sediment masses of sulphathiazole crystals, no bacteria, a few white cells. — Sulphathiazole and insulin were administered. After a few days the chemotherapy had to be suspended owing to severe vomitings. She received two blood transfusions, but her condition continuously got worse. On the 17th February she began to groan and complain about gastralgia. The abdomen was everywhere soft but diffusely tender to pressure. The temperature 38.4°, the pulse 96. On the 18th February her general condition was greatly affected. Non-protein nitrogen 80 mg %. The urine free from albumin and reducing substance. On the 21st February her temperature rose to 39° and harsh; crackling sounds were heard at both lung bases, for which reason the chemotherapy was resumed. The patient, however, got still worse and during the last days of her life lay with her gaze steadily riveted upwards and to the right. She died on the 24th February. 1944. Clinical diagnosis: reticulosis, myeloblast leukemia?

Table of blood values.

Year	Date	% hemo-glob.	Mill. red cells	Total white cells	Leukocytes			large monoc.	lymphocytes
					Non Filamented	Filamented	eos.		
1942	4.12	59	2.43	1500	4	18	1		77
	6.12	62	2.85	1300	3	29			68
	9.12			2700		29		8	52
	12.12			2300	7	27		6	60
	15.12	72	3.20	1500	26	11		4	59
	21.12	72	3.15	1950	9	18	2	4	67
1943	2.1			3100	9	43		2	46
	4.1	74	3.86	2700	10	40	1		49
	15.1	64	3.70	1600	21	22		3	51
	13.2			2600					
	16.2	72	3.60	4400	16	42	3	2	37
	24.9	82	4.00	2800					
	14.12	67	3.30	2300	1	4		8	87
	24.12	52	3.30	1500	1	9		4	86
	13.1	49	1.93	1500		6		3	91
	15.2	28	1.22	550		18			82
1944	17.2	38	1.12	1400	2	4		6	88

*Postmortem* 25th February. Slightly icteric. Cor: 390 grams. Moderate arteriosclerosis with rigid valves and slight sclerosis in the coronary artery. Pulm: rather small, pale. Edema. Marked arteriosclerosis in the aorta. Peritoneum: nothing noteworthy. Pharynx: fibrinous, diphtheric laryngopharyngitis. Oesophagus: Marked, yellowish grey, dry, chalky coating. Microscopically: The epithelium largely destroyed. The wall coated with

leukocytes, fibrin, bacteria and masses of fungi. The latter penetrate also into the outermost layers of the wall. The wall slightly infiltrated with leukocytes and round cells. Bacterial culture: Moderate growth of *B. coli* and enterococci, abundant growth of *Saccharomyces*. Stomach: The fornix part of the mucous membrane studded with papules, scarcely as large as a hempseed at most, in many cases surrounded by a hemorrhagic zone. In other parts a small number of papules. Microscopically: Focal concentrations of bacteria, masses of fungi and a small number of leukocytes in the outer parts of the mucous membrane. Duodenum, *intestinum tenue* et *crassum*: nothing noteworthy. Pancreas: somewhat rigid. Hepar: Numerous yellow-white foci, the largest being of the size of a hazel-nut, dry on the surface, with a diffuse border, in many cases surrounded by hemorrhagic zones. Microscopically: In the centre of the foci marked necrosis. Peripherally a zone of karyorrhectic leukocytes as well as abundant masses of fungi and bacteria. In some cases the foci are surrounded by granulation tissue with round cells, plasma cells and fibroblasts. Close to a small focus there is a fresh, mixed thrombus in the porta branch. Masses of bacteria in vessels and tissues. Bacterial culture: Abundant growth of Friedländer's bacillus, scanty growth of *B. coli*. Lien: Studded with foci macroscopically resembling those in the liver, but without a hemorrhagic zone. Microscopically the foci consist of an intensely necrotic centre and a peripheral zone with bacteria and decomposing leukocytes. Bacterial culture: Abundant growth of Friedländer's bacillus, *B. coli* and enterococci. Renes: In one of them macro- and microscopic necrosis of the papule tops with necrotic shreds in some calyces minores. The necroses are surrounded by a scanty fringe of leukocytes and, further peripherally, by round cells and plasma cells. In the necroses large masses of bacteria, which continue up into some ducts. Bacterial culture: Abundant growth of *B. coli* and enterococci. Vesica urin: diphtheric, purulent cystitis. Genitalia: nothing particularly noteworthy. Mening. cerebri: Slight pachymeningitis haemorrhagica interna. Cerebrum: nothing noteworthy. Vertebral marrow: Microscopically rather poor in cells. *Diagnosis*: Multiple abscesses of granulomatous character in liver and spleen, containing an abundance of Friedländer's bacilli. Cystopyelitis.

### Summary.

Report of the case of a woman aged 60, who was laid up with angina tonsillaris, accompanied by high fever and such marked difficulty in swallowing that diphtheria was suspected. At the same time, evidently from the same infection, she had an abscess on the left thigh, from which  $\beta$ -hemolyzing streptococci could be cultivated. Granulocytopenia, due to a severe lesion of the bone-marrow, was also observed. This lesion was presumably produced by a toxic

effect of the above-mentioned infection, though it may have existed before, thus facilitating the severe infection. In addition, a mild diabetes mellitus was detected. The granulocytopenia proved to be very resistant to treatment with blood transfusion as well as with yellow marrow per os and liver preparation parenterally. After hospital treatment for  $2\frac{1}{2}$  months she was discharged for continued nursing in her home.

Ten months afterwards she developed an ugly cystitis. It was then found that the granulocytopenia had become still more marked and that the bone-marrow lesion had increased in severity. It was not amenable to treatment, and after a month's nursing in hospital she was discharged.

Barely a month afterwards she was again admitted to the hospital. She had now only general symptoms, namely fever and a greatly affected general condition. After a week, however, abdominal pains, intense nausea and vomiting supervened. Her condition rapidly got worse and she died after ten days in hospital. She had succumbed to a sepsis, apparently induced chiefly by Friedländer's bacillus<sup>1</sup>, and a severe cystopyelitis. This cellular reaction may be considered to have been mainly due to the protracted septicemia and the inability of the body to give an adequate leukocytic response to the infection. A contributory factor was the peculiar reaction, noted by Hegler and Nathan, to Friedländer's bacillus, with a marked necrosis element.

The portal of entry of the infection was apparently the intestinal canal. Scattered concentrations of bacteria were in fact found in the stomach. Though unfortunately, they were not cultivated. This find may serve to bear out the above cited view of Baehr, Shwartzman and Greenspan regarding the predominantly abdominal location of infections with Friedländer's bacillus. In this case too no lung lesions were observed.

---

<sup>1</sup> There were scattered abscesses in liver and spleen of a curiously granulomatous character containing numerous Friedländer bacteria.

## Bibliography.

G. Baehr, G. Shwartzman and E. Greenspan: Bac. Friedländer abdominal infections due to perforative lesions of the intestinal tract. Mount Sinai Hosp. 4, 255, (1937). — C. Boettiger, M. Weinstein and J. Werne: Primary suppuration of liver due to Friedländer's Bacillus. J. A. M. A. 114, 1050 (1940). — P. Carnot, J. Dumont and E. Libert: Infections hépatobiliaires à bacille de Friedländer. Paris med. 1, 479, (1930). — C. Hegler and H. Nathan: Über Buday- und Friedländer-Bacillensepsis. Klin. Wochenschr.: 11, 1900, (1932).

---

From Biological Laboratories Medicinalco Ltd., Copenhagen.<sup>1</sup>

## The Rôle of Tyrosine in pernicious Anemia.

By

ERIK JACOBSEN and C. M. PLUM.

(Submitted for publication September 25, 1944).

Recently it is shown that a substance accelerating the ripening of reticulocytes is found in plasma and various organs, among which the liver is specially to be mentioned (C. M. Plum 1942 I). The concentration of the reticulocyte ripening factor in plasma varies from species to species, but in healthy adults only little variation is found from individual to individual (C. M. Plum 1943). The hitherto highest concentration found in that of ox plasma, the ripening index of which is arbitrarily fixed at 1.00. In normal human plasma the ripening index varies between 0.72 and 0.85 with an average of 0.77 [C. M. Plum (1942 II), Ruth Plum (1943)]. The plasma of children and menstruating women have shown higher values while lower values are found under certain pathological conditions, mainly in Graves' disease and in pernicious anemia.

Chemically the ripening principle is found to consist of at least two fractions, one of which being thermostable and the other

<sup>1</sup> The clinical investigations are kindly made by Chief physician Ole Bang M. D. (Medical Department, Centralsygehuset, Randers), Prof. Carl Holten M. D. (University clinic, Medical Department, Kommunehospitalet, Aarhus), Chief physician Esben Kirk (Medical Department, Amtssygehuset, Holstebro), Prof. E. Meulengracht M. D. (Medical Department B, Bispebjerg Hospital, Copenhagen), Chief physician E. Schiødt M. D. (Medical Department, Amtssygehuset, Aalborg), Prof. Carl Sonne M. D. (University clinic, Medical Department A, Rigshospitalet, Copenhagen) and Chief Physician Poul Schultzer M. D. (Medieinsk Poliklinik, Kommunehospitalet, Copenhagen), to whom the authors want to express their thanks.



thermolabile. Each fraction isolated is ineffective against the reticulocytes, only the combination is able to accelerate the ripening of reticulocytes (Erik Jacobsen & C. M. Plum 1942). The thermostable fraction is tyrosine or closely related to that substance (Erik Jacobsen & C. M. Plum 1942, Inger Gad, Erik Jacobsen & C. M. Plum 1944).

The chemical nature of the thermolabile fraction is not yet fully unveiled but it seems that some xanthine derivatives at least partly play a rôle in this fraction (Erik Jacobsen 1944). The thermolabile fraction is apparently formed in the stomach and in the upper part of duodenum (C. M. Plum 1944 I—II) and under co-operation with the reticuloendothelial system this fraction is activated with tyrosine or tyrosine-like substances and forms the reticulocyte ripening principle found in plasma (Erik Jacobsen & C. M. Plum 1943). No increase in the ripening power is found when tyrosine is added to normal plasma, but when the ripening index is lower than normal under the named pathological conditions or after blocking of the reticuloendothelial system, an addition of tyrosine to the plasma will increase the ripening index to normal figures. This fact suggests that the tyrosine metabolism is disturbed in some way in these diseases.

When the short review on the physiology of the ripening principle is summed up, the following facts are to be emphasised: An unknown thermolabile substance is formed in the stomach and in the upper part of the duodenum. This substance is connected with tyrosine which is a normal part of the food and forms thereby a principle active in the ripening of a certain stage of the development of the red blood corpuscles. This principle is stored in the liver and acts in the blood system. There is a striking resemblance between this development and Castle's theory regarding the physiology of the active principle against Addison's pernicious anemia and this resemblance is still more underlined through the already mentioned fact that the ripening index in plasma of patients with untreated pernicious anemia is considerably lower than that of normal individuals.

Stefan Jørgensen and C. M. Plum (1943) found the ripening index of a patient with pernicious anemia 0.53 (i.e. 67 p.c. of normal) and Ruth Plum (1943) found the ripening index of another patient 0.56; after adding tyrosine to the plasma, the index rose to 0.75

and similar results were subsequently obtained in other cases of pernicious anemia.

After treatment with liver extracts or dried stomach the ripening index of plasma increases to normal values along with the increase in erythrocytes and hemoglobine, and it remains normal as long as the treatment is adequate. In the patient of Stefan Jorgensen & Plum the ripening index rose to 0.92 in less than 12 days after the beginning of the specific treatment.

The reticulocyte ripening principle and the antipernicious principle cannot, however, be identical simply for the reason that the antipernicious principle in liver stands boiling for several hours while the reticulocyte ripening principle is destroyed after a few minutes.

Nevertheless it seems worth while to find out whether a connection exists between these two principles both acting on the development of the erythrocytes. It is not probable that the thermolabile fraction of the reticulocyte ripening principle is affected in pernicious anemia since the plasma of these patients can be fully reactivated by the addition of tyrosine. As pointed out above it is most likely that it is the tyrosine metabolism which is disturbed in some way.

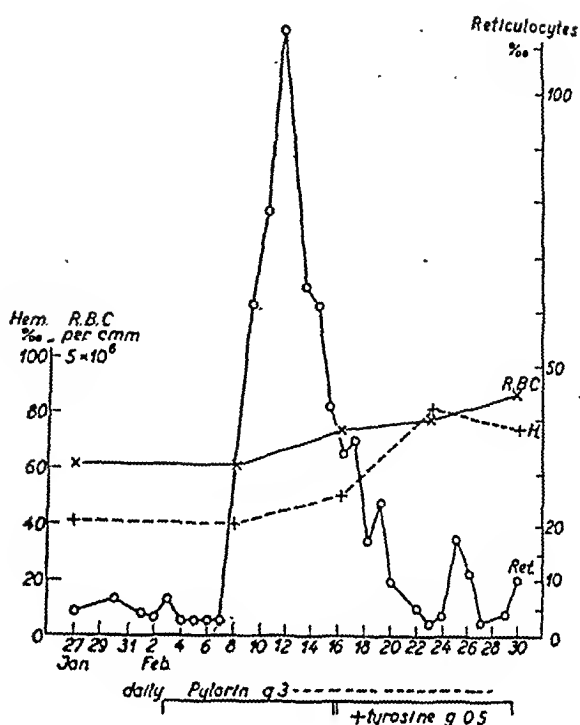
In a few papers tyrosine has been mentioned in relationship with liver extracts, erythropoiesis and pernicious anemia. B. M. Jacobson, Y. Subbarow and C. A. Fiske (1935) have found tyrosine in rather large amounts in active liver extracts, a finding which we too are able to confirm. The same authors state that tyrosine is able to induce a reticulocyte response in normal guinea pigs and finally Jacobs (1937) attributes to an oxygenating product of tyrosine (hallachrome or «red substance») a certain rôle in pernicious anemia.

So far as we know experiments with tyrosine in pernicious anemia have not been published and with the foregoing considerations as background it seems well indicated to try such an experiment.

The present investigation has been carried out in the following way:

Patients with untreated pernicious anemia were treated with a subadequate of desiccated, defatted, pyloric part of hog stomach. Pylorin «Meo», for a period sufficiently long to allow a marked

Patient No 1(R.H.)  
a T.F.N. 63 years



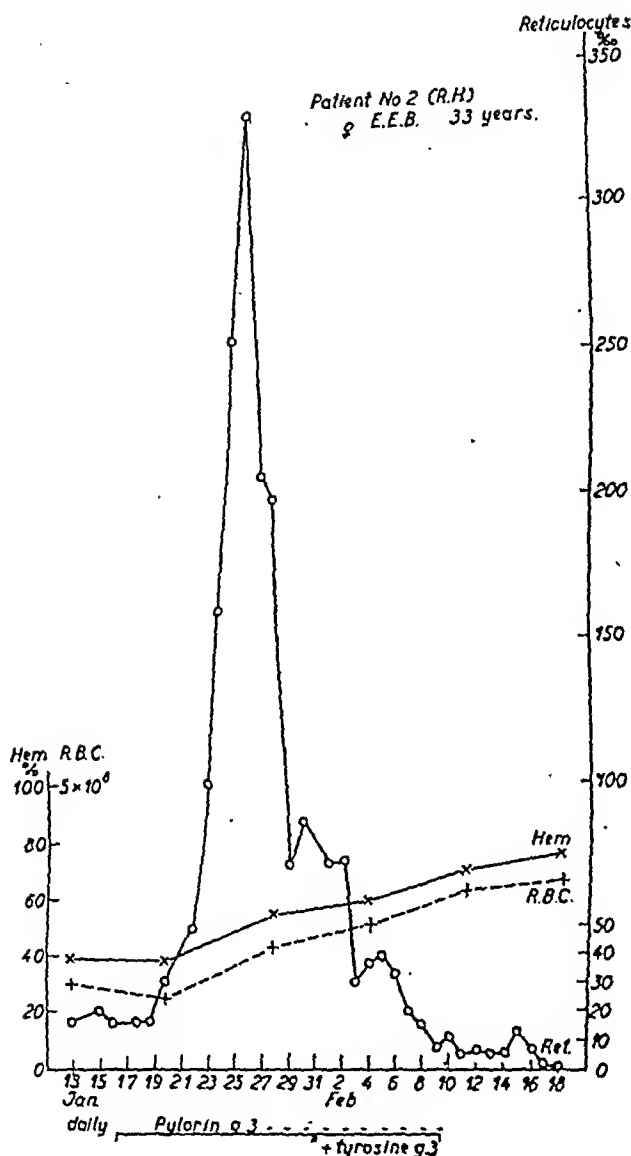
reticulocyte response to appear; then in a second period the same dose of Pylorin «Mco» was given with an addition of 0.5 g tyrosine per day. If the tyrosine plays a rôle in the antipericious complex, the effect of the Pylorin will be increased, and a secondary reticulocyte response must follow. When no secondary response can be observed, the reason may be one of two: either has the dose first given been adequate, or tyrosine has no effect on the antianemic principle. The first item can be controlled by giving a large dose of liver extract parenterally after the second period; if this is not followed by a reticulocyte response, the dose of Pylorin must have been maximal, and no reticulocyte response could be expected even if tyrosine had a considerable effect.

This series of experiments comprises 9 patients, and the results are summarized in Fig.'s 1—9.

The results obtained fall into two groups.

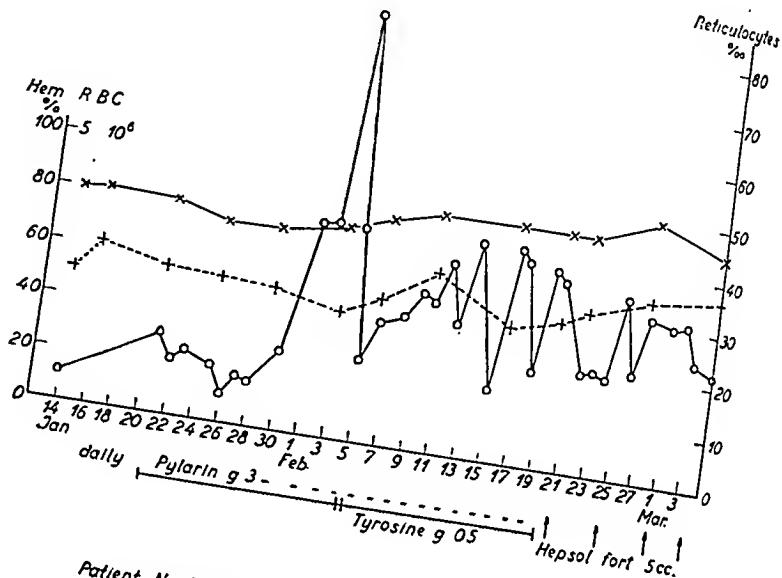
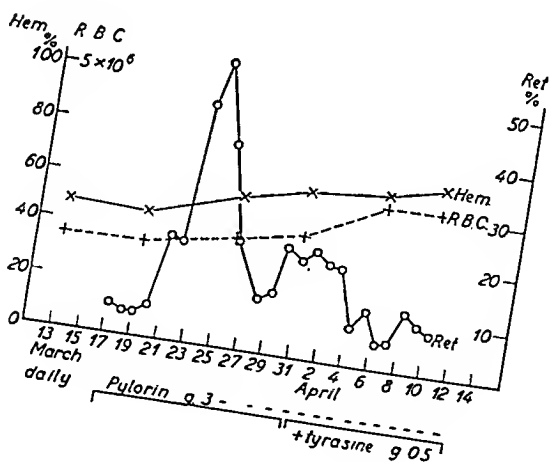
The patients in the first group, consisting of cases No.'s 5 and 7,

## THE RÔLE OF TYROSINE IN PERNICIOUS ANEMIA.



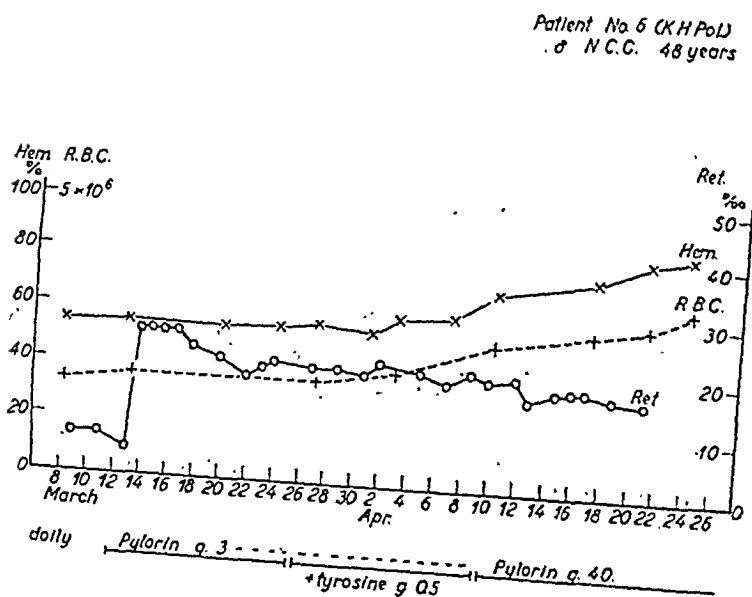
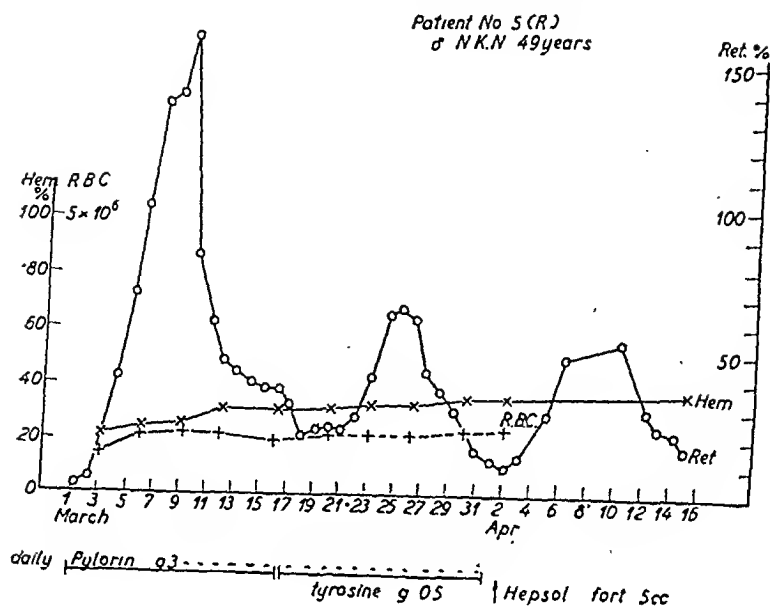
all show a marked reticulocyte response after addition of tyrosine to the dried pyloric powder. In these cases the added tyrosine has had a clear activating effect on the submaximal dose of the anti-pernicious preparation used. The secondary reticulocyte response in case 8 is seen as early as the second day after the administration of tyrosine. It is doubtful whether this response exclusively is due to the tyrosine or it is to be regarded as a delayed response from the Pylorin treatment, but the figures show here the same tendency

ERIK JACOBSEN and C. M. PLUM.

Patient No 3 (Aa EH)  
♀ OR 69 yearsPatient No 4 (H)  
♀ H.A.N 63 years

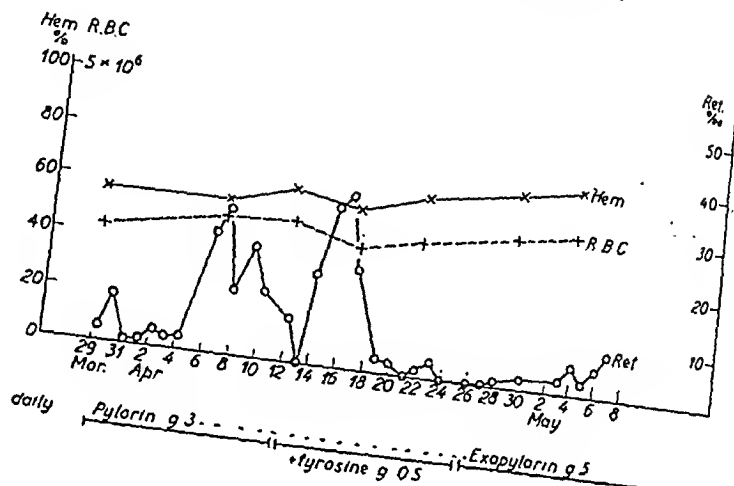
as in the cases 5 and 7, and most probably the response has some connection with the addition of tyrosine.

In the second group no definite secondary response is seen. In the cases 2, 3, and 6, it seems that the treatment with as little as the 3 gm. Pylarin daily has been adequate or nearly adequate.

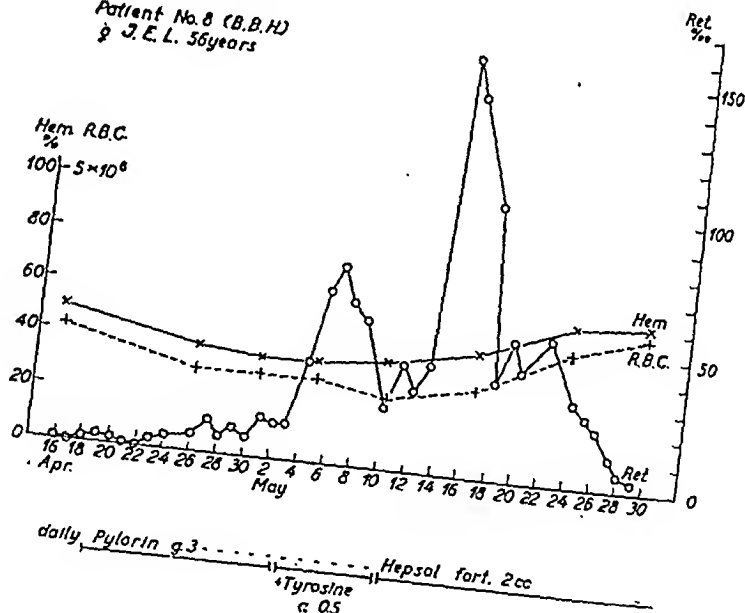


Patient No. 2 has shown an enormous reticulocyte reaction on the initial Pylorin dosage. Some slight fluctuations in the reticulocyte figures take place in the Pylorin-tyrosine period, but no proper reaction is seen, even when a rather large dose of liver extract

Patient No. 7 (B.B.H.)  
 ♀ B.A.A. 57 years



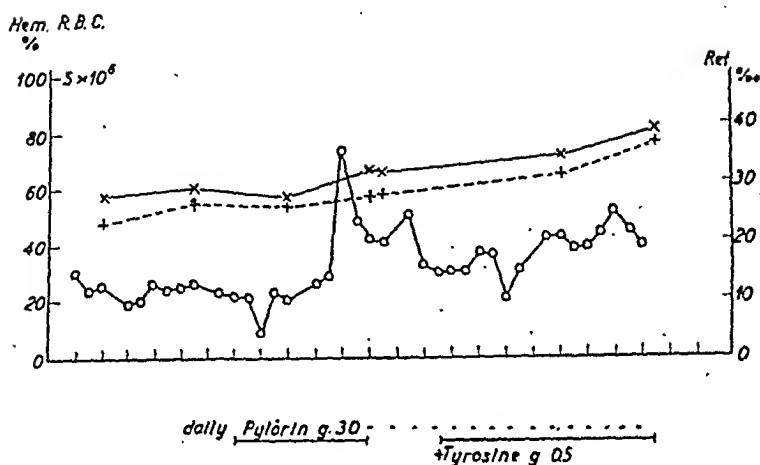
Patient No. 8 (B.B.H.)  
 ♀ J.E.L. 56 years



(Hepsol Fortior «Mco») is given in a third and final period. Patient No. 6 gives hardly any reticulocyte reaction at all, not even in the last period of 40 grammes Pylorin a day, which is a fairly high dose. It is to be noted here that the increase in hemoglobin and in

## THE RÔLE OF TYROSINE IN PERNICIOUS ANEMIA.

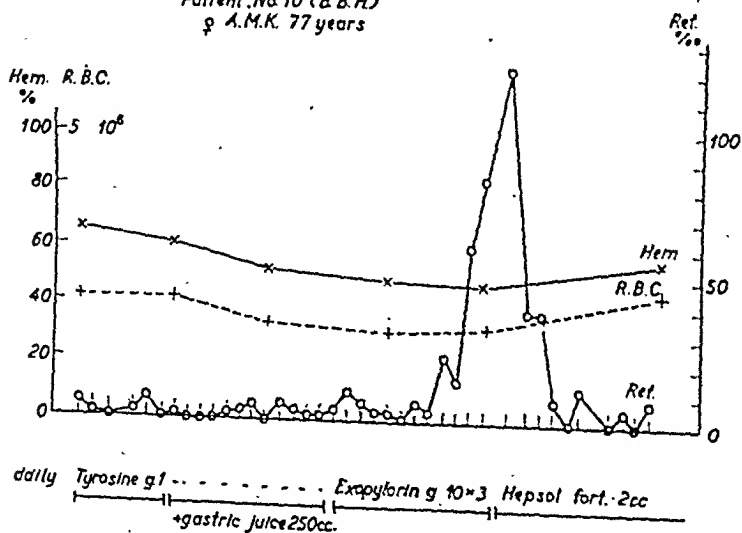
Patient No. 9 (Aa. A.S.)  
 ♀ K.P. 43 years



the number of red blood corpuscles does not begin until the addition of tyrosine to the Pylorin is made.

Patient No. 1 gives a reticulocyte reaction with a peak of 110 p.M., which is likely to be maximum after peroral treatment of a pernicious anemia beginning with 2 mill. red blood corpuscles per  $\text{mm}^3$ , and an increase of 2 millions in less than a month seems to be satisfying. It is probable that the treatment of this patient has

Patient No. 10 (B.B.H.)  
 ♀ A.M.K. 77 years





been adequate, and thus a secondary reaction after addition of tyrosine could not be expected. The two remaining patients, No.'s 4 and 9, give only small reticulocyte reactions, and so the preparation do not seem to be improved through the addition of tyrosine. To sum up these experiments it may be concluded that the therapeutic effect of dried pylorus can be increased by means of tyrosine, but not in all cases. It seems probable that tyrosine acts as a supplement to the extrinsic factor. Tyrosine is, however, not identical with the extrinsic factor itself; this is clearly demonstrated in the following experiment where tyrosine imbibed with gastric juice from normal persons failed to have any effect on the pernicious anemia. The result of this experiment is given in Table 10.

### Discussion.

The experimental facts hitherto available are the following:

1. Tyrosine or tyrosine derivatives form a part of the reticulocyte ripening principle.
2. Tyrosine injected into normal animals causes an increase in reticulocyte ripening index (C. M. Plum and Ruth Plum 1943).
3. Tyrosine gives a reticulocyte reaction in normal guinea pigs (B. M. Jacobson, Y. Subbarow and C. A. Fiske (1935)).
4. The tyrosine fraction of the reticulocyte ripening factor is less than normal in patients with untreated pernicious anemia, and
5. Addition of tyrosine to a submaximal dose of pyloric tissue given to untreated patients with pernicious anemia will in some cases induce a secondary reticulocyte reaction.

That tyrosine plays a rôle in the erythropoietic system is beyond discussion, since it is found as a factor in the reticulocyte ripening principle. But this involves only the very last step in the erythrocyte development, and we do not know if tyrosine has any accelerating effect on the earlier steps of the erythropoiesis.

The reticulocyte reaction does not necessarily point to an increased production of red blood corpuscles; a reticulocyte response may as well occur when the erythrocytes are put into circulation from the bone marrow in a more unripe state than normal. The secondary reaction observed in the three of our patients may therefore not be due to an increased effect of the antipernicious drug given, but it may as well be an unspecific reaction in a hyper-

sensitive erythropoietic system similar to that which is observed when normal guinea pigs are given tyrosine. So far we do not know if tyrosine has other effects on the erythropoiesis than as a fraction of the reticulocyte ripening principle.

Tyrosine is lacking in patients with pernicious anemia, since the ripening index in plasma is here found below normal and can be brought to normal values by addition of tyrosine to the plasma. When the patients are treated with liver extracts or with gastric tissue an increase in ripening index until normal figures is observed but this does not say anything about a possible effect of tyrosine on other symptoms than the ripening index, and as already emphasized the secondary reticulocyte reaction after tyrosine administration can be merely a nonspecific phenomenon.

In Graves' disease a similar decline in ripening index is observed. Very often, but not always, this disease is accompanied by a slight anemia. As the anemia is not a constant symptom, it looks most probable that tyrosine is not essential for the earlier steps in the development of the red blood corpuscles. The discussion on this disease can, however be postponed to a later occasion.

Why a deficiency of tyrosine occurs in pernicious anemia is difficult to say. The same symptom is seen in gastrectomised animals and the most obvious explanation is that the resorption of tyrosine is disturbed. In this connexion the attention is drawn to the aminopolypeptidase of Ågren (1942—1943) which is found in the stomach and may be absent in cases of pernicious anemia. The other possibility: a disturbed tyrosine metabolism, can of course not be excluded through the experiments hitherto made.

It will thus require a series of further experiments to enlighten the problems of the relationship between pernicious anemia and blood formation on one side and tyrosine on the other, but the present experiments show that some relation must exist.

### Summary.

In earlier experiments signs of a deficiency of tyrosine in pernicious anemia were found. We have made the present experiments in order to ascertain whether tyrosine has any supplementary effect on the regeneration of erythrocytes during the remission of pernicious anemia.

The main issue is that some of the patients with pernicious anemia showed a secondary reticulocyte reaction after the addition of tyrosine to a submaximal dose of dried pyloric tissue of hog stomach; in other cases, however, the addition of tyrosine had no effect.

Tyrosine has no effect when added to normal gastric juice. From this we conclude that tyrosine is not identical with the extrinsic factor, but that it is lacking in pernicious anemia; some of the symptoms may be due to the lack of tyrosine.

### Notes to the patients:

Patients 1—9 are treated in 1943.

Patient 10 is treated in 1944.

»Pylorin»: desiccated and defatted pyloric part of hog stomach.

»Tyrosine»: synthetic d-l-tyrosine in patients 1—9. l-tyrosine from casein in patient No. 10.

»Exo-Pylorin»: Pylorin to which is added extra extrinsic factor from liver.

»Hepsol Fortior»: Liver extract for parenteral use; 1 cm<sup>3</sup> corresponds to 100 grammes of liver.

Aa. A. S.: Medical Department, Amtssygehuset, Aalborg.

Aa. K. H.: Medical Department, Kommunehospitalet, Aarhus.

B. B. H.: Medical Department B, Bispebjerg Hospital, Copenhagen.

H.: Medical Department, Amtssygehuset, Holstebro.

K. H. Pol.: Medicinsk Poliklinik, Kommunehospitalet, Copenhagen.

R.: Medical Department, Centralsygehuset, Randers.

R. H.: Medical Department A, Rigshospitalet, Copenhagen.

### Literature:

- Gad, Inger, E. Jacobsen and C. M. Plum: (1944) *Acta Phys. Scand.* 7, 244. — Jacobs: (1937) *Jl. lab. clin. Med.* 22, 890. — Jacobsen, E.: (1944) *Acta Phys. Scand.* in press. — Jacobsen, E. and C. M. Plum: (1942) *Acta Phys. Scand.* 4, 272. — Jacobsen, E. and C. M. Plum: (1943) *Acta Phys. Scand.* 5, 1. — Jacobson, B. M., Y. Subbarow and C. A. Fiske: (1935) *New Engl. Journ. Med.* 212, 663. — Jørgensen, S. and C. M. Plum: (1943) *Ugeskrift for Læger* 105, 787. — Plum, C. M.: (1942 I) *Acta Phys. Scand.* 4, 259. — Plum, C. M.: (1943) *Acta Phys. Scand.* 5, 165. — Plum, C. M.: (1942 II) *Acta Med. Scand.* 112, 151. — Plum, C. M.: (1944 I) *Undersøgelser over Reticulocytmødningen in vitro*. Diss. Copenhagen. — Plum, C. M.: (1944 II) *Acta Med. Scand.* in press. — Plum, C. M. and Ruth Plum: (1943) *Acta Phys. Scand.* 5, 380. — Plum, Ruth: (1943) *Ugeskrift for Læger* 105, 1173. — Ågren, G.: (1942) *Arkiv för Kemi, Mineralogi och Geologi* 16 B No. 6. — Ågren, G.: (1943) *Arkiv för Kemi, Mineralogi och Geologi* 17 B No. 16.

(From the Medical Department III of Södersjukhuset, Stockholm. Head:  
Dr G. Kahlmeter.)

## An after-examination of operated and non-operated cases with «clinical symptoms of herniated disc».

by

LENNART KIRSTEIN.

(Submitted for publication September 25, 1944).

---

The purpose of the present investigation, which has been undertaken at the request of Dr Kahlmeter, is to ascertain the difference between operated and non-operated cases of the sciatic syndrome with röntgenological signs of a space restricting process in the spinal canal, as far as the late result is concerned, particular regard being paid to the subjective absence of symptoms. There is no knowledge available of any previous comparative investigation of this kind with the exception of after-examinations of cases subjected to operation for herniated disc and ligamentary root compression. Thus, in the material published by Craig (1) in the year 1939 (size not stated), 67 per cent of the patients were in good health and quite fit for work, 29 per cent suffered from less pain than prior to the operation and, finally, the result was unsatisfactory in 5 per cent of the cases. The observation time with regard to these patients equalled between 1 ½ and 2 years. Malmros (2) has submitted 54 patients operated on for prolapse of the disc and 12 with a ligamentary root compression to after-examination, preferably using a questionnaire. The observation time varied between 1—6 ½ years. He found that 67 per cent were healthy and altogether fit for work, 18 per cent being considerably improved and partly fit for work, 15 per cent being unfit for work.

Table I. Operated cases.

Case num.	Sex	Year of birth	Profession or occupation	Site of the compression	Duration of time of observation	Radicular pains	Paresis-thesias	Paresis or weakness in the affected leg	Subjective back symptoms	Resumed work after
1	Fem.	1895	Household work	L. 4—L. 5	3 years	—	(+)	—	—	1 month
2	Fem.	1896	Office clerk	L. 5-sacrum	3 years	—	+	—	+	6 months
3	Fem.	1901	Household work	L. 5-sacrum	3 years	(+)	(+)	—	—	3 months
4	Fem.	1910	Household work	L. 2—L. 3	3 years	(+)	(+)	+	—	6 months
5	Male	1890	Typographer	L. 4—L. 5	3 years	(+)	+	+	+	3 months
6	Male	1898	Mechanic	L. 4—L. 5	3 years	—	(+)	—	—	1 ½ month
7	Male	1901	Labourer	L. 3—L. 4	3 years	—	—	—	+	1 month
8	Male	1902	Labourer	L. 4—L. 5	3 years	(+)	—	+	—	6 months
9	Male	1903	Office clerk	L. 5-sacrum	3 years	—	—	—	+	1 month
10	Male	1903	Chauffeur	L. 5-sacrum	3 years	—	—	—	—	3 months
11	Male	1895	Engineer	L. 4—L. 5	2—3 years	—	+	+	—	3 months
12	Male	1895	Labourer	L. 4—L. 5	2—3 years	—	—	—	—	1 ½ month
13	Male	1896	Ex-labourer	L. 4—L. 5	2—3 years	(+)	—	—	+	—
14	Fem.	1901	Cashier	L. 4—L. 5	1—2 years	—	—	—	—	1 ½ month
15	Fem.	1903	Seamstress	L. 4—L. 5	1—2 years	(+)	—	—	+	3 months
16	Fem.	1906	Seamstress	L. 4—L. 5	1—2 years	—	—	—	+	3 months
17	Fem.	1916	Shop assistant	L. 4—L. 5	1—2 years	(+)	(+)	+	+	2 months
18	Male	1895	Labourer	L. 4—L. 5	1—2 years	—	—	—	—	3 weeks
19	Male	1896	Bank clerk	L. 5-sacrum	1—2 years	—	+	—	—	3 weeks
20	Male	1904	Electrician	L. 5-sacrum	1—2 years	—	(+)	—	—	5 ½ months
21	Male	1904	Dentist	L. 5-sacrum	1—2 years	—	—	—	—	3 weeks
22	Male	1906	Labourer	L. 4—L. 5	1—2 years	—	—	—	—	1 month
23	Male	1913	Hairdresser	L. 4—L. 5	1—2 years	—	—	+	+	5 months
24	Fem.	1913	Factory worker	L. 4—L. 5	1—2 years	—	—	+	—	3 months
25	Male	1899	Office clerk	L. 5-sacrum	< 1 year	—	—	—	+	2 months

Interpretation of signs: + = unimproved (— = improved) — = free from troubles  
 As regards Paresis, etc., and Subj. back symptoms, only the presence (— +) or absence (— —) of these signs have been tabulated in the table (owing to

Case num.	Sex	Year of birth	Profession or occupation	Site of the compression	Duration of time of observation	Radicular pains	Pares-thesias	Paresis or weakness in the affected leg	Subjective back symptoms	Resumed work after
26	Fem.	1906	Cashier	L 5-sacrum	3 years	—	—	—	—	6 months
27	Male	1884	Chauffeur	L 2—L 3	3 years	—	—	—	—	2 weeks
28	Male	1888	Labourer	L 4—L 5	3 years	—	—	—	—	2 weeks
29	Male	1892	Labourer	L 4—L 5	3 years	—	—	—	—	3 months
30	Male	1901	Labourer	L 4—L 5	3 years	—	—	—	—	discharged
31	Male	1909	Labourer	L 3—L 4	3 years	—	—	—	—	1 month
32	Fem.	1905	Household work	L 5-sacrum	2—3 years	(+)	—	—	—	—
33	Male	1879	Fix-labourer	L 5-sacrum	2—3 years	(+)	—	—	—	—
34	Male	1883	Postman	L 4—L 5	2—3 years	—	—	—	—	discharged
35	Male	1889	Typographer	L 4—L 5	2—3 years	—	—	—	—	2 months
36	Male	1893	Chauffeur	L 4—L 5	2—3 years	—	—	—	—	discharged
37	Male	1898	Labourer	L 5-sacrum	2—3 years	—	—	—	—	1 month
38	Male	1899	Office clerk	L 5-sacrum	2—3 years	—	—	—	—	4 months
39	Male	1907	Labourer	L 3—L 4	2—3 years	—	—	—	—	discharged
40	Fem.	1883	Household work	L 5-sacrum	1—2 years	—	—	—	—	4 months
41	Fem.	1885	Household work	L 2—L 3	1—2 years	—	—	—	—	3 months
42	Fem.	1907	Maid	L 3—L 5	1—2 years	—	—	—	—	6 months
43	Fem.	1912	Waitress	L 4—L 5	1—2 years	—	—	—	—	7 months
44	Male	1884	Surveyor of customs	L 4—L 5	1—2 years	—	—	—	—	1 month
45	Male	1886	Labourer	L 5-sacrum	1—2 years	—	—	—	—	1 ½ month
46	Male	1890	Mechanic	L 4—L 5	1—2 years	—	—	—	—	3 weeks
47	Male	1899	Labourer	L 4—L 5	1—2 years	—	—	—	—	2 months
48	Male	1903	Chauffeur	L 5-sacrum	1—2 years	—	—	—	—	3 months
49	Male	1901	Labourer	L 4—L 5	1 year	—	—	—	—	6 months

Interpretation of the signs under radicular pains and paresthesias:

+ = unimproved (—) = improved  
 + = symptoms newly added or deteriorated  
 — = symptoms neither before nor after operation (as regards non-op. cases; neither before nor after the first hospital stay).

As regards Paresis, etc., and Subj. back-symptoms, only the presence (+) or absence (—) of these symptoms has been denoted in the table (owing to inadequate information from the patients).

The present author's material comprises 49 patients, all treated at Åsö Sjukhus during the years 1939—1942. The time of observation has varied between 6 months and 3 years. The myelogram has been obtained with lipiodol in cases 2, 4, 5, 7, 8, 10 and 30, oxygen-gas having been used in the other cases. 25 have been submitted to operation, a space restricting process having been removed in all the surgical instances. The cause of the compression was protrusion or prolapse of a disc in 21 cases, being only a thickened ligamentum flavum in 4 (cases 6, 8, 11 and 17). All the non-operated patients have, during their stay at Åsö Sjukhus, undergone some form of physical treatment (viz., hard bed, baths, heat, Röntgen treatment). 5 of the patients in this group (cases 26, 27, 33, 35 and 38) have afterwards been treated with a plaster corset for a period varying between 1—3 months. One patient (case 26) then wore a leather corset for a year, another patient (case 27) is still wearing one. There is no difference in the two groups as to the duration of the subjective symptoms. All the patients have been after-examined by the author personally. They were interrogated as regards their subjective symptoms, as well as subjected to a neurological examination. Tables I and II give a survey of the material (viz., sex, age, profession, site of the compression, duration of time of observation, the facts concerning the pains and the paresthesias, subjective spinal symptoms, paresis or sensation of weakness in the affected leg, and the exact time at which work could be resumed).

### **Radicular pains, subjective and objective symptoms in the back.**

An attempt has been made to distinguish between the radicular pains<sup>1</sup> and those localised to the low back. 15 of the *operated* patients were relieved of their radicular pains (see Table III) immediately after the operation, 1 after a lapse of 1 ½ month, 1 after 5 ½ months (case 20: comparatively unchanged troubles after the operation. Accordingly, a new myelogram was obtained 4 months later, revealing the same picture as before the operation. Later, the patient became free from troubles after having worn a plaster corset for 1 month). Finally, 1 patient was not altogether

<sup>1</sup> In this connection the term radicular pains signifies those localised to the legs.

Table III.  
*Radicular pains.*

	Free from troubles	Improved	Not improved	Total
Op. ....	18	7	0	25
Non-op. ....	9	7	8	24
Total .....	27	14	8	49

$$\chi^2 = 11.0 \quad P = 0.01-0.001.$$

P indicates probability that the differences are due to chance, calculated by the  $\chi^2$ -analysis.

free from troubles until 2 years afterwards. No recidivism was noted in any of the patients who were free from troubles. Among the 9 non-operated patients, exempt from radicular pains, 2 had improved thus far immediately after the discharge from the hospital, 2 after 1 month, 2 after 3 months, 2 after  $\frac{1}{2}$  a year and 1 after 9 months. Transient recidivism had occurred in 2 instances. Among 8 of the unimproved patients (i. e. with severe pains at the after-examination) 5 had constant, 3 recidivating symptoms. 2 of the above-mentioned 9 patients had been submitted to corset treatment. As regards the other patients treated in this way, 2 revealed no improvement and 1 did.

When the operated and non-operated patients are compared with regard to freedom from radicular pains, 18 (i.e. 72 per cent) will be found to be free from troubles in the former group and 9 (i.e. 37.5 per cent) in the latter. The difference is statistically significant.

Among the operated patients free from radicular pains, 2 complained of slight pains at exertion, 3 of a feeling of tiredness, and 1 of stiffness in the low back. 4 of the improved patients belonging to this group had spontaneous or movement pains in the low back. As regards those free from radicular pains and not operated on, 5 had pains and 1 a feeling of tiredness in the low back. As regards radicular pains, 4 of the improved cases and 5 of the unimproved ones complained of back pains.

Thus, 12 of the operated cases (i.e. 48 per cent), and 3 of the non-operated ones (i.e. 12.5 per cent) were altogether free from radicular pains and subjective back symptoms. The difference is statistically probable (Table IV).

It would obviously be of interest to know whether the laminectomy in any way affected the troubles in the back. A survey of the



**Table IV.**  
*Radicular pains and subjective back symptoms.*

	Free from troubles	Not free from troubles	Total
Op. ....	12	13	25
Non-op. ....	3	21	24
Total .....	15	34	49

$$\chi^2 = 5.69 \quad P = 0.02-0.01.$$

When the number of cases in any group was equal to or less than 5, Yates' correction was used.

**Table V.**  
*The relationship between the laminectomy and the subjective back symptoms.*

	Laminec- tomy 2 arches	Laminec- tomy 1 arch	Partial laminec- tomy	Hemila- minec- tomy	No laminec- tomy	Total
Ache .....	1	2		1	2	6
Tiredness ....	1	2				3
Stiffness .....					1	1
No back troubles ...	1	5	3		5	14
Total .....	3	9	3	1	8	24

subjective spinal symptoms of the patients, whether subjected to laminectomy or not, will be seen in Table V. Notes are lacking in 1 instance (case 1) in the operation report as regards the performance of laminectomy, although this appears likely when considering the year in which the patient was operated (1940). However, this patient did not complain of any back troubles whatsoever. As a matter of course, this case has not been included in the table. — It will be seen that among the 16 patients who have been subjected to laminectomy in some form or other, 9 were altogether free from troubles at the after-examination. Only 4 of the remaining patients complained of real back pains. 2 of the 8 patients who had not undergone laminectomy suffered from back pains, i.e. 25 per cent, the same figure as in the former group. The material is, of course, much too restricted to permit the drawing of any conclusions from the figures obtained. It should be noted that the patient who had undergone hemilaminectomy (on L 3, L 4 and L 5) prior to operation did not complain of back pains but afterwards.

suffered from constant pains in the low back (case 17). One patient (case 14) had felt a pronounced stiffness in the back half a year after the operation. She became free from troubles after having worn a plaster corset for 3 months, being free from symptoms since half a year ago.

10 of the operated patients disclosed a bilateral contracture of the erector trunci, 3 had a unilateral one. The corresponding figures with regard to the non-operated patients were 16 and 6, respectively. 3 patients in the former group reported soreness at palpation of the erector holds in the lumbosacral region on one or both sides, the latter group having 8 such instances.

The subjective and objective spinal symptoms of the patients may, of course, be connected with an insufficiency of the spinal muscles and a spondylosis deformans process, respectively. However, since no röntgenogram of the spine has been taken at the after-examination, the author has been unable to enter upon the question of the connection in this respect.

### Paresthesias.

In the present paper, numbness, pins and needles and chill have been classified as paresthesias. The result of the examination is illustrated in Table VI. In 2 of the operated cases, paresthesias had occurred postoperatively. In one of them (case 19), the 1st sacral root was found at operation to be strongly adherent to the herniated disc: «the root was loosened, being rather traumatized in the process». Immediately after the surgical intervention the patient noticed decreased sensibility on the outside of the left leg and in the dorsum of the foot, as well as a sensation of numbness in the little toe. His condition gradually improved somewhat. The other

Table VI.  
*Paresthesias.*

	Par. neither at the 1st exam. nor at the after-exam.	Free from troubles	Im- proved	Un- changed	Newly added	Total
Op. ....	5	10	6	2	2	25
Non-op...	4	10	3	3	4	24
Total	9	20	9	5	6	49

patient (case 2) complained of numbness sometimes, under the soles of both feet (no notes in the operation report of any trauma of a root). Both patients showed diminished sensibility corresponding to S 1.

### Paresis.

At the after-examination, 5 of the operated patients revealed a more or less pronounced paresis within the peroneus region in the affected leg with a decrease of the active force at dorsal flexion and pronation (cases 4, 5, 8, 16 and 23). None of the non-operated patients now suffered from any paresis. The paresis had been ascertained preoperatively in only 1 case (23) among the above-mentioned operated patients. The following status was found in the records in 1 instance (case 16): »no objective paresis but is unable to stand on tiptoe». A note had been made in the operation report of a lesion of the dura and a nerve root. According to the records, no paresis had been found in 2 instances (cases 4 and 8) before the operation, while in the remaining case (5) notes are lacking in the records in this respect. The paresis was not discovered until after the surgical intervention (acc. the patient and the records from Vanförestalten). 2 of the operated cases and 2 of the non-operated ones had a paresis within the peroneus region at the original examination which was unascertainable at the after-examination.

3 of the operation patients and 2 of those not operated on complained of weakness or tiredness in the affected leg. However, a distinct paresis or an affection causing a decrease in the active force was only found in 1 case (33). This patient had clinical symptoms of severe arthrosis deformans coxae on the corresponding side.

---

Thus, 6 of the operated cases (i.e. 24 per cent) and 3 of those not operated on (i.e. 12.5 per cent) were free from radicular pains, subjective back symptoms, paresthesias, and paresis or weakness in the affected leg. The difference is, accordingly, statistically probable (Table VII).

Table VII.

*Radicular pains, paresthesias, subjective back symptoms, paresis or weakness in the affected leg.*

	Free from troubles	Not free from troubles	Total
Op. ....	6	19	25
Non-op. ....	3	21	24
Total .....	9	40	49

$$\chi^2 = 6.50 \quad P = 0.02-0.01.$$

### Sensibility.

The patients with some kind of disturbance to their sensibility at the original stay at the hospital or at the after-examination are set down in Table VIII. At the after-examination, the sensibility to touch, pain and temperature has been tested. In the majority of the cases, notes are lacking in the records as regards the factor or factors submitted to examination the first time the patient was treated at Åsö Sjukhus. When denoting the segmentary extension of the disturbance to sensibility, Foerster's scheme has been followed. Anaesthesia, analgesia or termoanaesthesia have not been ascertainable in any single case at the after-examination, except for a reduction in the factors concerned.

12 of the operated patients are said to have had reduced sensibility preoperatively, which improved or altogether disappeared in 7 cases, increased in 3, remained unchanged in 1, and was localized to another segment postoperatively in another case. No disturbance to sensibility had been found prior to surgery in 3 instances, which has, however, now been established by the present author. In 1 case no remark has been made in the records regarding the sensibility. Also in this instance, reduced sensibility was found at the after-examination. As regards the non-operated patients, 11 had reduced sensibility at their first stay at the hospital. This remained unchanged in 3 cases, was now ascertainable in 6 cases, and had increased in 2. Finally, the author had noticed reduced sensibility in 2 cases where this had not been discovered earlier. Case 17 is particularly noteworthy from the point of view that postoperative hypersensibility to pain and temperature had been added.

The fact that a reduced sensibility has increased or been added

Table VIII.  
*The status of sensibility.*

Case num.	1st examination	After-examination	
1	part of L 5	no remark	
2	no notes	parts of S 1 and S 2	a.f.
3	S 2	L 3—S 3	t.
4	parts of L 3, S 1 and S 2	part of S 1	a.f.
5	parts of S 1 and S 2	parts of L 5—S 2	a.f.
6	S 1	no remark	
7	parts of S 2	no remark	
8	parts of S 2	L 3—S 2	a.f.
13	parts of L 3, S 1, S 2 and S 3	part of L 5	a.f.
15	no remark	parts of L 5, S 1 and S 2	a.f.
16	parts of S 2 bilat.	part of S 2 left	a.f.
17	no remark	L2—S 3 hypersensible p. and temp.	
19	no remark	S 1	p. and t.
20	part of S 1	no remark	
24	S 1	S 1	a.f.
25	part of S 1	no remark	
26	S 2	no remark	
32	part of S 1	parts of L 3 and L4; L5—S2	a.f.
33	no remark	L 2—S 4	a.f.
34	part of S 1	no remark	
35	part of S 1	no remark	
36	part of S 1	part of S 1	a.f.
37	part of S 2	parts of L 5 and S 1; S 2	a.f.
39	part of S 1	no remark	
41	part of L 5; S 1	no remark	
42	L 5; part of S 1	no remark	
44	part of L 3	part of L 3	p. and temp.
45	no remark	S 1	a.f.
46	part of L 5	part of L 5	p.

t. = touch, p. = pain, temp. = temperature, a.f. = all factors.

postoperatively may, perhaps, appear rather strange. This may, in 1 instance (case 19), be accounted for by the trauma of the root during the surgical intervention. Apart from the possibility of a similar trauma (whether overlooked by the operator or not noted in the operation report), an explanation must, probably, be sought for, as regards the other cases, in a greater neurological

Table IX.  
The status of the ankle jerk.

Case num.	1st examination		After-examination		The affected side
	right	left	right	left	
1	—	—	—	—	left
2	+	+	+	—	right + left
3	+	—	+	—	left
4	—	+	—	+	right
5	+	(+)	(+)	—	left
6	(+)	+	—	—	right
8	+	—	+	—	left
9	+	+	+	—	left
10	+	—	+	—	left
11	+	+	+	—	right
12	+	(+)	+	+	left
16	—	—	—	—	left
18	+	—	+	(+)	left
19	+	—	+	—	left
20	(+)	+	+	+	right
22	—	—	—	—	left
24	+	—	+	+	left
25	—	+	—	+	right
26	+	—	+	(+)	left
32	(+)	+	—	+	right
34	—	—	—	—	right
35	+	(+)	+	+	left
37	+	(+)	+	(+)	left
40	+	+	—	(+)	left
45	+	—	+	—	right
48	+	—	+	+	left

(+)= weakened reflex.

accuracy at the after-examination of the patients than at the original examination at the hospital. — The above-mentioned remark also applies to postoperative paresis.

#### Ankle and knee jerks.

The ankle jerk was lacking preoperatively on both sides in 3 cases among the operated ones, on one side in 8 cases. In 4 cases the reflex was weakened unilaterally (the corresponding figures of the non-operated cases are 1, 3, 3)—see Table IX. The status was

Table X.  
*The status of the knee jerk.*

Case num.	1st examination		After-examination		The affected side
	right	left	right	left	
1	(+)	—	+	+	left
3	+	(+)	+	+	left
12	+	+	+	—	left
27	(+)	+	+	+	right

unchanged at the after-examination in 9 instances, an improvement having occurred in 4, and a deterioration in 2 (the corresponding figures of the non-operated cases are 3, 3, 1). 3 patients, regarding whom no reflex anomaly had been ascertained preoperatively according to the records, now showed no excitability on one side. A similar occurrence was noted in 1 of the non-operated cases. One of the operated patients (case 11) is of particular interest. Thus, the reflex was lacking in the unaffected leg without the patient having felt any symptoms of sciatica. A contralateral loss of the reflex also occurred in one non-operated case (45). However, the patient had suffered from sciatica in the now healthy leg 20 years ago.

As far as the knee jerk is concerned (see Table X), the reflex is said to have been weakened or lacking uni- or bilaterally at the original examination in 3 of the total number of cases. The reflexes of these patients were now normal. At the after-examination, the loss of a reflex was ascertainable only in one patient (case 12) who had, nevertheless, showed normal response preoperatively.

### Ability to work.

It will be seen from Tables I and II that 1 of the operated patients had not been able to work after the surgical intervention owing to sciatic symptoms. 2 of the non-operated patients had not resumed work; in 1 case (32) forbidden work on account of severe hypertonia, in the other case (33) unable to work owing to pains in the legs one year before the admission to hospital (simultaneous arthrosis deformans coxae). Among the non-operated cases, 3 were unfit for work at the after-examination owing to sciatica. 2 of

Table XI.  
*The ability to work.*

	Fit for work	Unfit for work	Total
Op. ....	24	1	25
Non-op. ....	19	3	22
Total .....	43	4	47

$$\chi^2 = 0.43 \quad P = 0.9-0.8.$$

the patients belonging to this group had changed work, only one of them having had to do so on account of physical troubles. Thus, excluding case 32 and case 33, 24 of the 25 operated patients (i.e. 96 per cent) and 19 of the 22 non-operated ones (i.e. 86.1 per cent) were fit for work. There is no statistical difference. (See Table XI). Among the operated patients, 6 had resumed their work 1 month after the surgical intervention, 14 after 3 months, and 5 after half a year. As regards the non-operated patients, 10 resumed work after 1 month, 6 after 3 months, 5 after half a year, and, finally, 1 not until 7 months after the discharge from the hospital.

The present author has not entered upon the question of whether the patients (those improved and not improved, in particular), had been at work during the whole time of observation, since this is not only dependent on the possible absence of troubles but also, to a great extent, on the kind of work and the psychical state of the patient.

### Summary.

A comparative after-examination has been performed of 25 operated patients and 24 non-operated ones suffering from the sciatic syndrome with röntgenological symptoms of a space restricting process in the spinal canal. In 21 of the operated cases, the compression was due to herniated disc (-prolapse), in the remaining 4 cases being due to hypertrophy of the ligamentum flavum. The duration of the time of observation varied between 3 years and 6 months. — 72 per cent of the operated cases and 37.5 per cent of those not operated upon were free from radicular pains at the after-examination, disclosing a statistically significant difference. When also the subjective back symptoms are taken into account, 48 per cent in the former group and 12.5 per cent in the latter



were free from troubles. 24 per cent of the operated, 12.5 per cent of the non-operated cases were completely free from subjective troubles. The difference was statistically probable in both the latter instances. — 96 per cent of the operated patients and 86.4 per cent of the non-operated ones were found to be fit for work at the after-examination. — Furthermore, the patients have been examined with regard to paresthesias, paresis within the peroneus region, disturbances to sensibility, ankle and knee jerks, and the possible effect of laminectomy on the spinal troubles.

### Literature.

- 1) Craig, W. McK.: The present status of the protruded disk syndrome. *Compt. rend. III Congrès Neurolog. Intern. Copenhague 1939*, page 752.
  - 2) Malmros, R.: Den lumbale discusprolaps og ligamentaere rodcompression. — Einar Munksgaard, København 1942, page 108.
-

*Acta Medica Scandinavica.* Vol. CXX, fasc. I—II, 1945.

From the Anatomical Department, Karolinska Institutet, and the Department for Metabolic Research, Wenner-Grenska Institutet, Stockholm University, Stockholm.

## **The Rythmical Variations of the Liver Glycogen and the Pyruvic Acid of the Blood in Experimental Obstructive Jaundice.**

By

**Y. EDLUND and HJ. HOLMGREN.**

(Submitted for publication September 15, 1944).

---

The fact that the ligaturing of the common bile duct leads to a decrease in the liver's percentage of glycogen has long been known. Thus a marked decrease of the liver's glycogen percentage was obtained by von Wittich (1875) in experiments on doves, rabbits and dogs, and by Külz and Frerich (1876) with rabbits and guineapigs. It is of interest to note that the latter authors could show by glucose injections on animals with bile obstruction, that in spite of the obstruction the liver had to a certain extent not lost its power of glycogen production. Dastre and Arthus (1889) ligatured the hepatic duct on dogs, and found that a glycogen decrease arose in that liverlobe which belonged to the ligatured duct. Later, (1929) even Ravdin found that a ligaturing of the common bile duct lead to a liver glycogen decrease. Normal animals had a percentage of 5.5 in their livers, while those of operated animals showed after 2—6 weeks a sinking to about 1 %. On histological examination the glycogen was shown to be in the main centrally localised within the liverlobes. He discovered further that the liver, though damaged through the ligaturing of the common bile duct, had the ability to synthetise and store glycogen. Varela, Duomarco and

Munilla (1930) studied the effect which experimental obstructive jaundice had upon the liver's supply of glycogen and fat in different animal species, ie, the rat, rabbit, dove and cat. In the white rat a diminution by nine-tenths of the normal liver glycogen value occurred already an hour and a half after the operation, and after six hours the glycogen had totally disappeared. After 14—45 days the glycogen began to reappear in the liver. With regard to the fat, they were able to prove a decrease in the rat liver during obstructive jaundice. By ligaturing the hepatic duct a general diminution in the entire liver's glycogen supply was caused, this being however most pronounced in the lobe belonging to *that* duct.

• On glucose being introduced into the operated animals the liver-cells, notwithstanding their disturbed outer secretion, showed the ability of glycogen storage. According to Bollman and Mann (1936), dogs are able to live 6—15 weeks after the development of experimental obstructive jaundice. In jaundice of shorter duration the liver is large, becoming smaller the longer the stasis. Microscopic observation showed a dilation of the bile ducts, and atrophical changes in the liver cells, chiefly periportal. Their statement that animals could live longer on a carbohydrate diet is of interest. Bernhard (1938) performed his experiments with ligaturing of the common bile duct on different animals, namely dogs, rabbits, guinea-pigs and rats, with all of which he could prove a liver glycogen decrease. According to his point of view this is caused by the fact that, after ligaturing of the common bile duct, fat (about 90 %) cannot be resorbed, and carbohydrates must therefore be used in combustion. He further points out that the increased bile supply in the liver caused by the stasis activates the diastase, which leads to an increased liver glycogen metabolism. He could further prove that a liver, damaged before operation through phlorrhizin poisoning and therefore poor in glycogen, was less resistant against that trauma which an experimental obstructive jaundice constitutes. Glucose treatment should according to Bernhard increase the liver resistance, and in experiments with this therapy he obtained fewer grave liver damages through ligaturing of the main bile duct than in tests without glucose. Banks and Sears (1939) produced experimental obstructive jaundice on dogs, and found, as earlier authors had shown, a decided decrease in the liver's percentage of glycogen. In the liver, histological changes arose in the form of

acute and subacute pericholangitis. In some cases small necroses with polynuclear infiltrate together with fatinfiltrate were found. Lastly can be mentioned that according to Johnsson, Ravdin, Vars and Zintel (1940) an increased fat supply occurs simultaneously with the decrease of glycogen in the liver of dogs killed 13—35 days after a ligaturing of the common bile duct.

From the above, it is evident that there is a general agreement that a ligaturing of the common bile duct leads to a diminution in the liver's supply of glycogen. Varela and his colleagues found that this diminution in e.g. the rat, occurred soon after the operation. It can possibly be remarked against their work that the number of animals used in their experiments was small, so that the result must therefore be viewed with some reservation. The entire testseries comprised only 14 animals, which were killed  $1\frac{1}{2}$  hours to 45 days after the operation. In this work we have wished to investigate the disturbances arising in the liver's normal rythm after experimentally produced obstructive jaundice. As known, (Forsgren 1927—1935, Holmgren 1931—1936, Ågren, Wilander and Jorpes 1931, and others) there are normal 24-hourly variations in the liver's percentage of glycogen and fat. Thus the liver of e.g. rats, under the assimilatory phase (nighttime) is rich in glycogen, while it is poor in glycogen during the day (dissimilatory phase). With regard to the fat, and even the liver's percentage of gallgranula, the case is reversed through the different hours of the day and night (Holmgren). We have in our experiments made chemical analyses of the liver's glycogen percentage, and histologically examined sections with regard to fat percentage and other pathological changes. Furthermore, we have studied the variations of blood pyruvic acid in experimentally produced jaundice. Pyruvic acid is, as known, an important intermediary product of carbohydrate metabolism, and it should therefore be of some interest to examine the changes in pyruvic acid percentage brought about by the serious liver damage to which an obstructive jaundice leads.

### Material and Method.

As test animals large white rats have been used, weighing between 150 and 200 grams, of both sexes, though in the main male animals. The operation — ligaturing of the common bile duct —

was performed under ether anaesthetic, silk thread being used in the most cases, catgut in the remaining. The common bile duct was then carefully dissected free from the blood vessels, so that no vessel branches should be included. The animals quickened rapidly after the operation, and showed no mentionable affect. Even a week after the operation their condition and appetite were good. Those symptoms noticable after the operation were a jaundice-like colouring of the skin, and a strongly yellow colour of the urine.

The chemical analyses made were glycogen determination according to Sjögren, Nordenskjöld, Holmgren and Möllerström (1938) and the determination of the percentage of pyruvic acid in the blood according to Lu-Lövgren (See Möllerström 1943). The pyruvic acid determinations were made at the Department for Metabolic Research at the Wenner-Gren Institute in Stockholm. Further, a histological study of the liver was made, whereby pieces of liver were fixed in 3 % bariunichloride (Forsgren 1927—1935), absolute alcohol and formol. The formol-fixed portions were fat-stained with Scharlach R, and nucleusstained with Mayers acid haemalum. The pieces fixed in alcohol were stained with Best's glycogen staining method, and lastly the bariunichloride fixed pieces were stained according to Mallory. Further, and ordinary haematoxalin-eosin staining was used.

The animals were killed through decapitation 2, 3, 4 and 7 days after operation. Blood from the vessels of the neck was immediately collected for pyruvic acid determination. Thereafter pieces of liver were dissected out for glycogen analysis and histological examination. Of those rats which were allowed to live 2—4 days after the operation, some were killed at 10 a.m. and the rest at 10 p.m. (each group consisting of 5—9 animals). In that series, however, in which the animals were examined 7 days after operation, they were killed with 4-hourly intervals throughout the day and night, that is to say at 6 a.m., 10 a.m. 2 p.m., 6 p.m., 10 p.m. and 2 a.m. (each group including 7—10 animals). Parallel with this last experiment the pyruvic acid percentage of normal animals was determined (5—8 animals per group). The blood was obtained through heart puncture, and a slight ether anaesthetic was given so that the puncture should cause no excitement.

The formulae used in the statistical workings are given in earlier works by Edlund and Holmgren (1939—1940).

## Ovn Inwestigations.

## I. Normal animals.

No liver glycogen values from normal rats have been especially taken for this work, as the liver rythm of these animals has earlier, and with larger material, been examined by Holmgren (1936). When thereto Seckel and Kato (1938) in experiments on white rats obtained in the main equivalent charts to those of Holmgren, we

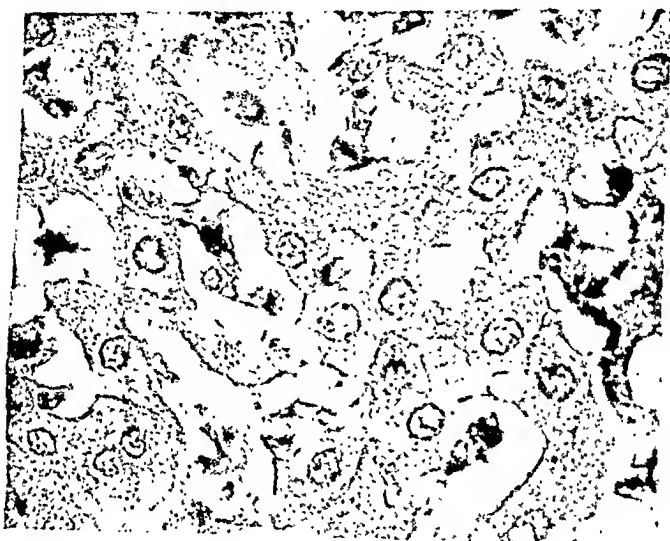


Fig. 1. Enlarged v. Kupfer cells in liver from animals killed 2 days after ligature of common bile duct. Fixative: 3 %  $\text{BaCl}_2$ . Staining: Mallory. Magnified 750 times.

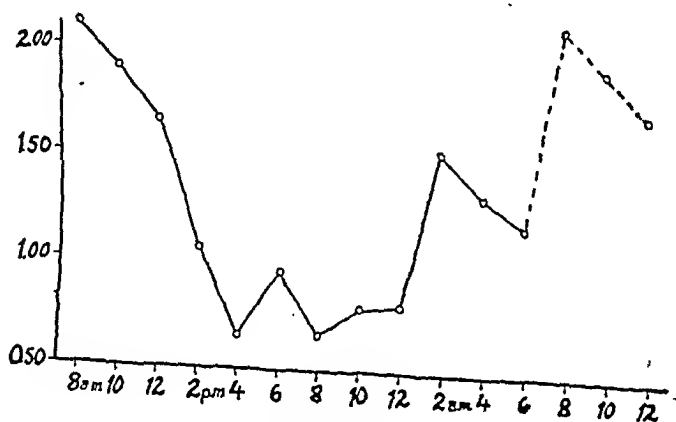


Diagram I.

Variations in liver glycogen of the rat according to Holmgren 1936.  
 Abscissa. Time.  
 Ordinata. Liver glycogen in gm per kilogram body weight.

have decided that these could be used in our investigations as control curves. The normal liver rhythm of the large white rat is as shown in diagram 1. This shows a marked glycogen minimum during the day, and a distinct maximum during the night. In the former phase the liver is found to be largely in dissimilation, while in the latter assimilation plays the greater part.

Table I.

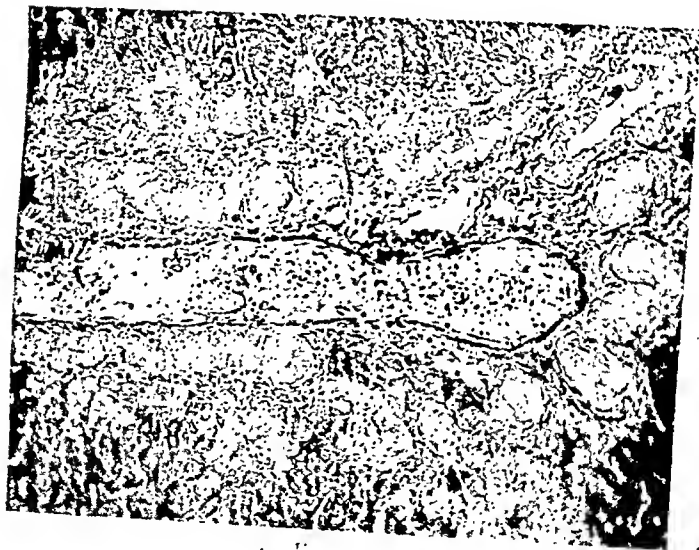
The Pyruvic acid percentage in blood from Normal Animals.

	mg %		mg %		mg %
6 a.m.	5.87	10 a.m.	3.79	2 p.m.	4.52
	1.78		4.80		4.55
	1.75		5.26		4.38
	5.37		4.02		5.26
	6.30		6.40		4.47
	<hr/>		<hr/>		<hr/>
average:	5.41	average:	4.85	average:	4.61
	mg %		mg %		mg %
6 p.m.	3.00	10 p.m.	2.75	2 a.m.	5.27
	3.05		4.00		4.69
	2.73		2.70		4.17
	4.57		4.20		4.02
	4.68		3.96		4.98
	1.70		2.80		
	4.61				
	4.42				
	<hr/>		<hr/>		<hr/>
average:	3.97	average:	3.25	average:	4.51

The variations in the blood's pyruvic acid from normal animals are shown in table I, diagram II. Each point in the chart is based on 5—8 results from blood taken through heart puncture. In the specimen taking we have given the animals a short (2—3 mins.) ether anaesthetic. As is known, an anaesthetic causes the breaking down of glycogen, and this method may cause an increase in the blood's pyruvic acid percentage. To examine whether this was the case under the short and superficial anaesthetic used, rats were decapitated at 10 a.m. and 6 p.m., and an investigation as to the pyruvic acid percentage of blood from neck vessels was made. The values obtained by this method did not differ from those obtained through heart puncture under anaesthetic. It seems to us therefore



a



b

Fig. 2. Obvious increase of the larger periportal bile ducts.  
a. Liver from animal killed 4 days after operation.  
b. Liver from animal killed 7 days after operation.  
Fixative, staining see Fig. I. Magnified 160 times.



hardly possible that the anaesthetic thus used should in any greater degree have disturbed our values.

In the chart over the pyruvic acid's normal variations it is shown that the curve sinks slowly throughout the day, reaching a minimum at 10 p.m., thereafter rising steeply to a maximum at 6 a.m. The difference between maximum and minimum is 2.16 mg %, this having been statistically determined. ( $T = 5.3, P < 0.001$ ). As shown in diagram I and II, the pyruvic acid curve runs largely parallel with that of normal liver glycogen.

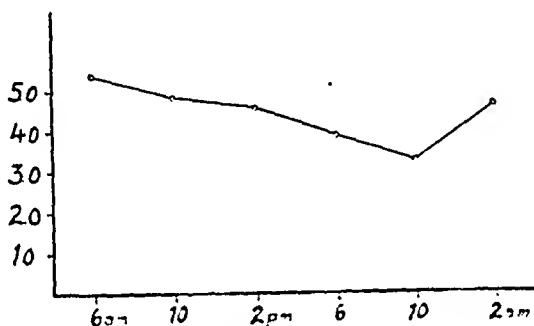


Diagram II.

The pyruvic acid's normal variations in the blood.

*Abscissa.* Time.

*Ordinata.* mg %.

## II. Experimental animals.

### A. The liverglycogen and pyruvic acid's condition after ligaturing of the common bile duct.

#### 1. Two days after operation.

The animals examined by us have been killed at 10 a.m. and 10 p.m. We have chosen these hours because at the first the liver is in the dissimilatory phase, while at 10 p.m. the assimilatory phase is beginning.

The resulting values are shown in table II. The liverglycogen at 10 a.m. is 0.60 %, and at 10 p.m. 0.84 %. Any greater difference between the values can thus not be discovered. Such is even the case with regard to the pyruvic acid which at respective hours shows values of 3.27 mg % and 3.82 mg %.

Table II.  
Two days after Operation.

<i>10 a.m.</i>		
<i>Animal No.</i>	<i>Liver glycogen %</i>	<i>Pyruvic acid mg %</i>
1457	0.95	3.51
1458	0.27	3.82
1459	0.68	2.96
1460	0.34	3.56
1461	0.77	2.52
	<u>average: 0.60</u>	<u>average: 3.27</u>
<i>10 p.m.</i>		
1468	0.57	2.82
1469	0.17	2.77
1470	3.54	2.96
1471	1.63	2.82
1532	0.36	4.60
1533	0.45	4.66
1534	0.00	5.39
1535	0.00	4.50
	<u>average: 0.84</u>	<u>average: 3.82</u>

Table III.  
Three days after Operation.

<i>10 a.m.</i>		
<i>Animal No.</i>	<i>Liver glycogen %</i>	<i>Pyruvic acid mg %</i>
1453	0.46	3.00
1454	0.57	2.35
1455	0.35	2.78
1456	0.31	3.16
1555	0.00	4.78
1556	0.00	3.81
1557	0.00	4.07
1558	0.00	4.20
1560	0.00	3.92
	<u>average: 0.19</u>	<u>average: 3.56</u>
<i>10 p.m.</i>		
1519	0.00	1.76
1523	1.23	—
1526	0.44	1.76
1527	1.64	1.73
1528	0.89	1.78
1529	0.35	1.50
1530	0.00	—
1531	0.32	1.56
	<u>average: 0.61</u>	<u>average: 1.95</u>

## 2. Three days after operation.

The average value for liver glycogen at 10 a.m. is 0.19 %, and at 10 p.m. the corresponding value is 0.61 %. The difference is in this case somewhat larger than in the previous test, but cannot be proved ( $T = 2.0$ ,  $P > 0.05$ ). The average values of the pyruvic acid at respective hours are 3.56 mg % and 1.95 mg %. The difference, 1.61 mg % can in this case be statistically proved. ( $T = 3.81$ ,  $P < 0.001$ ).

Table IV.  
Four days after operation.

10 a.m.		
Animal No.	Liverglycogen %	Pyruvic acid mg %
1536	0.25	4.94
1537	0.19	6.51
1538	0.18	2.93
1539	0.64	2.83
1540	1.49	7.34
1541	1.22	7.70
	<hr/> average 0.66	<hr/> average 5.38
10 p.m.		
Animal No.	Liverglycogen %	Pyruvic acid mg %
1463	2.28	2.52
1464	2.58	4.93
1465	3.60	2.96
1466	2.10	3.72
1467	3.45	3.87
	<hr/> average 2.80	<hr/> average 3.60

## 3. Four days after operation.

In this test the liverglycogen's average values at 10 a.m. and 10 p.m. are respectively 0.66 % and 2.80 %. We find thus that the liverglycogen of the former animals still stands at a low level, whereas that of the animals killed at 10 p.m. shows a decidedly higher value. The difference between these values is 2.14 %, this difference being statistically provable. ( $T = 5.7$ ,  $P < 0.001$ ). The average values of the pyruvic acid at 10 a.m. is 5.38 mg % and at 10 p.m. 3.60 mg %. The difference of 1.78 mg % cannot in this case be proved. ( $T = 1.7$ ,  $P > 0.1$ ).

Table V. (Continued p. 119).

Seven days after operation.

<i>6 a.m.</i>		
Animal No.	Liverglycogen %	Pyruvic acid mg %
1577	1.03	4.48
1578	1.21	6.48
1579	0.99	5.49
1436	0.00	5.90
1437	0.67	4.70
1438	2.04	—
1439	2.59	4.70
1440	1.80	4.61
1441	0.56	4.17
	<hr/> average 1.21	<hr/> average 5.07

<i>10 a.m.</i>		
Animal No.	Liverglycogen %	Pyruvic acid %
1379	0.60	1.79
1380	1.02	2.50
1381	1.75	3.01
1382	0.63	2.34
1383	1.07	2.98
1443	0.74	5.79
1444	0.81	5.01
1445	0.22	4.75
1446	2.58	4.71
1447	1.55	4.55
	<hr/> average 1.10	<hr/> average 3.74

## 4. Seven days after operation.

In this experiment series we have killed animals at six different hours (6 and 10 a.m., 2.6 and 10 p.m. and 2 a.m.) The results are shown in tables V, VI and diagrams III, IV.

With regard to the variations in the liverglycogen in these tests, these are, as shown in diagram III, relatively slight. The glycogen is least in those animals killed at 2 p.m. and 6 p.m. The remaining values lie in the main on an equal level. To procure a larger material, we have combined the glycogen values of animals killed at 6 a.m. and 10 a.m. in one group, in another group those of animals



Fig. 3. Multiple bile necroses in liver from animal killed 7 days after operation. Fixative and staining, see fig. 1. Magnified 90 times.

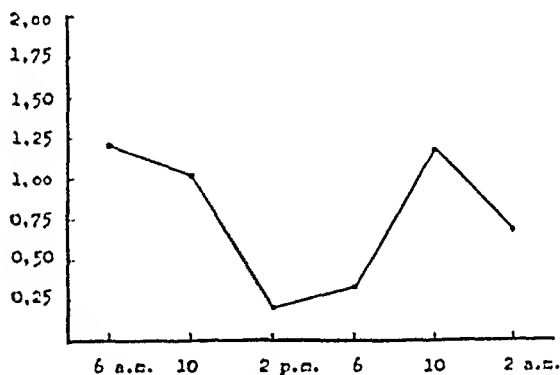


Diagram III.

The liver glycogen of the rat 7 days after operation.

*Abseissa.* Time.

*Ordinata.* Percentage of liver glycogen.

killed at 2 p.m. and at 6 p.m. and to a third those of animals killed at 10 p.m. and 2 a.m. The values thus obtained are to be found in table VI.

As shown in the table, the average value of the liverglycogen is lowest in group 1. The difference between this value and the corresponding value in group 2 is  $0.57 \pm 0.174$  %, and in group 3  $0.86 \pm 0.168$  %.

Table V. (Continued).  
Seven days after operation.

Animal No.	2 p.m.	
	Liverglycogen %	Pyruvic acid mg %
1384	0.11	3.99
1385	0.12	5.75
1386	0.10	4.80
1387	0.73	4.98
1388	0.16	5.52
1414	0.69	3.26
1415	0.15	2.04
1416	0.20	2.80
1417	0.07	2.78
1418	0.00	2.65
	<hr/> average 0.23	<hr/> average 3.86

Animal No.	6 p.m.	
	Liverglycogen %	Pyruvic acid mg %
1403	0.40	—
1404	0.17	—
1405	0.13	4.19
1406	0.14	4.73
1407	0.16	4.17
1419	1.15	4.70
1420	0.46	4.09
1421	0.27	2.61
1422	0.23	2.11
	<hr/> average 0.35	<hr/> average 3.94

Animal No.	10 p.m.	
	Liverglycogen %	Pyruvic acid mg %
1426	1.10	3.29
1428	2.54	2.19
1448	0.64	2.80
1449	0.79	2.80
1450	0.67	1.96
1451	1.43	1.56
1452	0.95	1.69
	<hr/> average 1.16	<hr/> average 2.33

Animal No.	2 a.m.	
	Livervglycogen	Pyruvic acid mg %
1411	0.30	3.00
1412	0.18	5.95
1413	0.21	3.46
1429	0.15	3.26
1430	0.86	—
1431	1.65	2.29
1432	0.54	2.29
1433	0.33	3.77
1434	1.93	2.54
	<u>average 0.68</u>	<u>average 3.32</u>

Table VI.

Group	Animals killed	No of. animals	Percentage of livervglycogen. ( $m \pm 2$ )
1	2pm. and 6pm.	19	$0.29 \pm 0.021$
2	10pm. and 2am.	16	$0.86 \pm 0.173$
3	6am. and 10am.	19	$1.15 \pm 0.167$

As seen, the differences between the various groups are in both cases greater than 3 times the standard error. The difference between groups 1 and 2 is up to 4 times as great as the standard error. These facts are of importance as the skewness of the series corresponding to groups 1 and 2 is so great. Though, as shown, the difference between the groups is nevertheless considerably larger

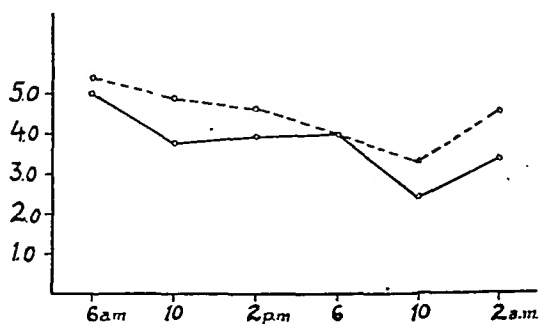


Diagram IV.

The variations in blood pyruvic acid; of normal animals -----  
of animals killed 7 days after operation. ———

Abcissa. Time.  
Ordinata. mg %.

than 3 times the standard error, one is forced to the opinion that the given decrease of liver glycogen at 2 and 6 p.m. cannot merely be coincidental.

The pyruvic acid variations are also shown in table V, diagram VI. This curve follows largely parallel with that of the normal animals, though in comparison with this somewhat lower. The difference (2.74 mg %) between the maximum (5.07 mg %) and the minimum (2.33 mg %) in the pyruvic acid percentage of the experiment animals can be statistically proved. ( $T = 7.2$ ,  $P < 0.001$ ).

It is of interest to note that the pyruvic acid varies rhythmically, largely in the same manner as in normal animals, and this though the liver glycogen in the experiment animals shows very small variations. It seems to us therefore probable that the fluctuation in the pyruvic acid percentage is not altogether due to the liver's carbohydrate metabolism. When according to Jorpes, Ågren and Wilander (1931) even the muscle glycogen shows rhythmical variations, it is possible that even these fluctuations are of importance in the pyruvic acid's variations.

### B. Histological Examination.

To procure an opinion as to the condition of the liver tissue, we have histologically examined the presence of those parenchymatous injuries caused by gall stasis. We have further in histological sections studied the relationship between the liver glycogen and liver fat.

#### 1. *Two days after operation.*

With regard to the liver glycogen, this is as a rule localized to those cells nearest to the central vein. Liver fat appears in all livers in sparse amount.

In eight cases out of thirteen examined, solitary to several small necrotic areas were found. In the liver cells round about the necroses were found, as a rule, larger quantities of fat than in other cells.

In several of the examined livers a fair degree of roundcell infiltration was observed round the perilobular vessel branches. Such infiltrations are however normal in liver from the rat.

It is of interest to note that we in two cases found extraordinarily large v. Kupfer cells. The feeling arose that they were in



these cases oedematous. In about half the cases even solitary liver-cell mitoses were found.

As regards the interlobular connective tissue, no definite increase could be observed. In two out of thirteen livers, however, a small but certain increase of the perilobular bile ducts was noted. The liver capillaries were throughout swollen with stagnant secretion.

## *2. Three days after operation.*

In the majority of the livers there was very little glycogen. This was found in solitary cells without definite locality within the lobules. In one case it was found stored in the cells round the central vein. Liver fat appeared in sparce to richer amounts, regardless of the time at which the animals were killed. In those cases in which a larger supply was found, this was deposited mainly within the peripheral parts of the lobules.

Necroses were found in a majority of livers. These were however scarce, stretching over a small area. Even in these cases single up to a fair number of mitoses were observed. With regard to the v. Kupfer cells, these were in a couple of cases decidedly enlarged.

In the examined livers there was no definite increase in the connective tissue. With regard to the bile ducts, we found in four cases of seventeen a certain — in one case fair — increase of the interlobular bile ducts.

## *3. Four days after operation.*

The liverglycogen has as a rule no definite localization within the lobules. A definite glycogen deposit was found in only four cases in the cells round the central vein.

In all but two of the livers a sparce to fair amount of fat was found, this with no definite localization within the lobules. In the two cases mentioned, no fat could be discovered at all.

With regard to the presence of necroses, we have in only three cases out of eleven discovered any necrotic areas in our microscopic sections. Mitoses were found in amounts ranging from a few to a fair number in about half the cases examined.

The connective tissues show in these cases a somewhat stronger reaction than in earlier examined livers. A still stronger reac-

tion was shown in the bile ducts. In seven livers a definite, sometimes moderate, increase in the number of larger bile ducts was found (see fig. 2).

#### 4. Seven days after operation.

The liver glycogen appeared as a rule in slight degree. It was found concentrated within the central zone of the lobules in only thirteen cases out of the total number. In the remaining cases the glycogen was distributed throughout the entire lobule.

With further regard to the fat, this appeared in rich amount in two cases, more moderately in twenty-nine. In the remainder, however, it was present in but sparse amount. The fat was found as a rule within the peripheral parts of the lobules.

Necroses appear mostly in larger number than in animals killed 2—4 days after operation (see fig. 3). In a comparison of livers between animals having lived seven days after operation, but killed at different hours, it was found that necroses appear in equally large quantities in all.

Regarding the presence of mitoses, it must be mentioned that decidedly fewer cell divisions were found throughout in the livers from animals killed seven days after operation, than in those from animals killed two to four days after operation.

It was found that of those livers in which the common bile duct had been ligatured during seven days, a definite increase of the interlobular connective tissue had taken place. In some cases this increase was markedly strong, in others only slight. Even the lesser bile ducts show a decided increase in number, in some cases relatively small, in others large. In the latter cases the newly-built bile ducts formed a strong interlobular layer.

In all the livers the bile capillaries were wide, and it could often be noted that the liver cells were small and rent apart. In a comparison between sections from  $\text{BaCl}_2$ -fixed livers from animals killed two to four days after operation, and similar sections from rats killed seven days after operation, it seems to us to be of interest that in the latter cases a smaller amount of intracellular gall granula appear — as a rule — than in the former.

In some cases a histological section showed a decided cirrhotically transformed liver with increased connective tissue and bile

ducts (cholestatic cirrhosis picture). A large number of round cell infiltrations was observed, but these occur, though in small quantities, even in normal livers. Further, purely necrotic areas were found, together with areas where the liver cells were small, rent apart, and strongly degenerated.

### Discussion.

After a ligaturing of the common bile duct on rats it was found that when the animals were killed two and three days after the operation at 10 a.m. and 10 p.m. the livers percentage of glycogen was remarkably low. This could have been caused either by the gallstasis as such, or by the fact that the animals had not yet recovered from the shock of the operation. As the liver, from a histological view, showed in these cases only relatively minor parenchymatous injuries, and as the liver glycogen on the fourth day after operation rose to about 3 % (at 10 p.m.), it seems probable that the low glycogen percentage was caused by the operation as such. Naturally, the importance of the gall stasis cannot be overlooked. According to v. Wittich (1875) and Bernhard (1938) the bile increases the ferment activity, and thereby hastens the glycogenolysis. Even Seckel (1938) has in his *vitro* experiments shown that bilesalts increase the glycogenolysis.

On the fourth day after operation, a difference in the glycogen percentage between animals killed at 10 a.m. and 10 p.m. was found, and this has been statistically proved. In animals killed seven days after operation, this difference was however not so prominent. The lowest values were found in animals killed at 2 p.m. and at 6 p.m. (see diagram III). This sinking in the liver glycogen curve is in all probability no mere coincidence, not with standing the skewness in part of the material. The low glycogen percentage must be caused by the gallstasis which has also brought about severe pathological-anatomically observable parenchymatous injuries. In some cases these have led to a picture cirrhotical likeness.

With regard to the pyruvic acid percentage in the blood, this is similar at all hours in animals killed two days after operation, a fact which is probably caused by the operational shock. Three days after the operation there is already a decided difference in pyruvic

acid between animals killed at 10 a.m. and at 10 p.m. This difference is thereafter even, regardless of the length of time after operation at which the animals were killed. It is of importance, however, to mention that the pyruvic acid values of animals killed two to three days after operation are throughout lower than those of animals killed four to seven days after ligaturing of the common bile duct. This difference would seem to be caused by the fact that the animals have only after the fourth day overcome the shock of the operation. The percentage variations of the pyruvic acid throughout the twentyfour hours in animals killed seven days after operation and in that of normal animals usually run parallel with each other, the minimum being at 10 a.m. and the maximum at 6 a.m.; the only difference between the two curves being that that of the experiment animals lies lower than that of the normal animals.

The attained results show that the liver glycogen two to three days after operation is in the main similar in animals killed at 10 a.m. to that of animals killed at 10 p.m. On the fourth day after operation the difference in liver glycogen between the two series is far greater. If this is a temporary difference, or if it is a true expression of the rythmical function of the liver under normal conditions it is difficult to say. With consideration to the results of the experiments with animals killed seven days after the operation, it seems however more probable to us that the discussed difference in the liver glycogen percentage is to be sought in the liver's rythmical activity.

The amount of liver glycogen in animals killed seven days after operation varies, as shown in diagram III, rythmically throughout the twentyfour hours. The least amount of glycogen (dissimilatory phase) is found in the daytime, and it is richest in those animals killed during the evening and night. As has already been mentioned, the curve's minimum can be proved. In a comparison between this curve and that of normal animals, according to Holmgren (1936), a certain similarity is noted between the two. The curve of the experiment animals does not, however, run absolutely parallel with that of the normal animals. This can most likely be explained by the fact that the former curve partly is based on fewer points than the latter, partly is composed of figures taken from animals with pathological livers. It is therefore not surprising that the two curves do not

tally in every detail. The result which in this case is of the greatest interest is that we still seven days after operation find rhythm in the liver's carbohydrate metabolism. Of interest too are the variations in the blood's percentage of pyruvic acid. As early as the third day after operation, this is lower in animals killed at 10 p.m. than in those killed at 10 a.m. This difference is thereafter constant in the remaining groups.

The variations in the pyruvic acid percentage in animals killed seven days after operation are shown in diagram III, and the values lie only slightly lower than do the corresponding values of normal animals. The results of our experiments show therefore that the liver rhythm, regardless of the severe damage caused by the ligaturing of the common bile duct, is constant, though the liver's glycogen capacity is decidedly lower than normal. Even the blood pyruvic acid's twentyfour hourly variations in experiment animals follow the corresponding curve for normal animals, though as a rule on a lower level. This is probably due to the fact that the liver's glycogen capacity is greatly reduced, and thereby even the eventual pyruvic acid which results out of the liver's carbohydrate metabolism.

The fact cannot be overlooked that the animals' appetite is diminished as a result of the operation, and that this possibly even effects the pyruvic acid percentage of the blood. The definite twentyfour-hourly rhythm to which the blood's percentage of pyruvic acid is subjected, seems, as the liver's glycogen store is at the time of these experiments minimal, to be probably an expression of the muscle tissue's rhythmical carbohydrate metabolism.

Our experiments have therefore shown that the liver's rhythmical function with regard to the variations in glycogen amount, as well as the changes in the blood's percentage of pyruvic acid, remain constant notwithstanding the liver injury caused by a biliary stasis. This circumstance seems to us clearly to show how important and how fast rooted in the organism is the rhythmical working principle.

It may seem curious that the liver rhythm is continued notwithstanding the fact that the organ's excretory duct is ligatured. The gall stasis under these experiments should cause a complete filling of the liver cells with secrete granulae, and thereby make impossible all other cell activity. During the first days after operation this was probably the case, but after hand the cell emptied it's

secrete into the blood stream, and thus causing jaundice. Through this intravasal secretion the liver glycogen's rythmical variations are made possible. Under an examination of the  $\text{BaCl}_2$ -fixed liver sections from animals killed seven days after operation, and from such killed two to three days after operation, larger amounts of secrete granulae were usually found in the latter.

From the histological examination we found already under the second day after operation in one or two cases a slight increase in the perilobular gall ducts, simultaneously with a varying amount of bile necroses in a number of cases. The longer the stasis lasted, the more strongly marked became these facts. At the same time, the perilobular roundcell infiltration increased. It is interesting to note that the number of mitoses appeared to be greatest three to four days after operation. After this period the liver cell's power of regeneration lessened.

The histological investigations show that the liver injury caused by the gall stasis is proportional to the length of time during which the stasis has lasted, and that injuries of about equal grade occur in the separate cases from each group. It has therefore seemed to us most suitable to collect and compare the results in the given manner.

---

These investigations have been carried out with money from the Therese och Johan Anderssons Minne» fund.

### Summary.

In the preceding work the liver glycogen's and blood pyruvic acid's rythmical variations have been investigated, after an experimentally produced obstructive jaundice. Further, the pathological state occurring in the liver after this injury has been histologically examined. Large white rats of both sexes (though mainly male) have been used in these experiments, and the following results have been obtained.

1. The blood's percentage of pyruvic acid in normal animals shows rythmical variations through the twenty-four hours, with a maximum at 6 a.m. and a minimum at 10 p.m. This curve runs largely parallel with that of normal liver glycogen.

2. Animals killed 2—3 days after operation show low liver glycogen values and any rhythm with regard to amount cannot be traced. The blood's percentage of pyruvic acid two days after operation shows largely equal values regardless of whether the animals were killed in the morning or evening. On the third day after operation, a definite difference appears in the blood's percentage of pyruvic acid between animals killed morning and evening — a difference which is constant even four to seven days after operation. The pyruvic acid values of the operated animals are slightly lower than those of normal animals, but even in the former a certain rhythm can be observed. With regard to the glycogen in animals killed seven days after operation, this lies usually on a higher level than in those animals killed two to four days after operation, this being probably explainable by the fact that the latter animals have not yet overcome the operational shock. Regardless of the sunken liver glycogen values of experimental animals, a liver rhythm can be plainly observed.

3. The grave liver damage caused by the ligaturing does not hinder the liver's rhythmical function. Thus can rhythmical changes in the liver's percentage of glycogen and in the blood's percentage of pyruvic acid be observed seven days after operation.

4. The longer the duration of the stasis, the more strongly marked are the damages to the liver. In animals killed seven days after operation, a large number of necroses are found, together with a definite increase in the interlobular connective tissue and with in some cases a cholestatic cirrhosis picture.

5. The liver's regenerative ability decreases as the stasis lengthens. The number of mitoses in the liver is less in animals killed seven days after operation in comparison with animals killed three to four days after operation. The regenerative ability would therefore seem to be greatest three to four days after operation.

### References.

- Banks and Sears 1939: Amer. J. Digest. 6, 83. — Bernhard 1938: Klin. Wschr. 10, 1761. — Bollman and Mann 1936: Amer. J. Physiol. 116, 214. — Dastre and Arthus 1889: Arch. de Physiol. 21, 473. — Edlund and Holmgren 1939: Z.f.d. gesamte experim. Med. 107, 26. — Edlund and Holmgren 1940: Z.f.d. gesamte experim. Med. 107, 275. —

Forsgren, 1927: Mikroskopiska och experimentella leverundersökningar Diss. Stockholm. — Forsgren 1927: Z. Zellforsch. 6, 647. — Forsgren 1929: Skand. Arch. Physiol. 55, 144. — Forsgren 1935: Acta Soc. Suecanae 62, 1. — Holmgren 1931: Z. Mikrosk.-anat. Forschg. 14, 632. — Holmgren, 1932: Z. mikrosk.-anat. Forschg. 32, 306. — Holmgren 1936: Studien ü. 24-Stundenrhythmische Variationen des Darm Lungen- und Leberfetts. Diss. Stockholm. — Johnsson, Ravdin, Vars and Zintel 1940: Arch. of Surg. 40, 1104. — Külz und Frerich 1876: Pflügers Arch. 13, 460. — Möllerström 1943: Das Diabetesproblem, Stockholm. — Ravdin 1929: J.A.M.A. 93, 1193. — Seckel 1938: Endocrinology 23, 751. — Seckel and Kato 1938: Arch. of Pathol. 25, 347. — Sjögren, Nordenskjöld, Holmgren and Möllerström 1938: Pflügers Arch. 240, 427. — Varela, Duomarco und Munilla 1930: Z. f. d. gesamte experim. Med. 72, 457. — v. Wittich 1875: Centralblatt f. d. med. Wissenschaft 13, 113. — Ågren, Wilander and Jorpes 1931: Biochem. Journ. XXV, 777.

---



From the Medical Dept. (Physician-in-Chief: — Dr. med O. Bang) and the Roentgenological Dept. (Physician-in-Chief: — A. Holtermann) of Diakonhjemmets Sykehus, Vinderen pr. Oslo.

## On gastritis.

By

ASBJØRN HOLTERMANN & HELGE MYHRE.

Submitted for publication to the norwegian editorial board 26:th of February 1943, in the hands of the Editor on the 24th of Nov. 1944.

---

Although gastritis has been acknowledged as a disease for more than a century, and in spite of its central position in gastric pathology, the problems of gastritis are still far from exhausted. This fact has several reasons. — It was a great inconvenience to the pathologists that the gastric mucosa goes to destruction very quickly after death. This difficulty, however, was evaded when Faber introduced his method of fixation immediately after death. Greater experience was gained when resection of the stomach as a treatment for ulcer came *en vogue*. Extensive studies of freshly fixed, surgically removed specimens have by now been performed, first and foremost by Konjetzny and his pupils, in Norway by Dahl. The results obtained are well known and comprises the stressing of the antral gastritis as an important, independent malady and as a conspicuous feature of the ulcer disease. The interrelation of gastritis and the ulcer disease is, however, not yet established. For a time the theory prevailed that the erosions of the gastric mucosa might evolve into ulcers, but this hypothesis has later on been dropped.

In his classification Dahl distinguishes between the chronic and the acute gastritis. The latter may appear independently, or

as an exacerbation of the former: it is characterised by hyperemia, oedema, and polynuclear cell infiltration of the mucosa, and formation of erosions. The chronic gastritis is marked by the infiltration of lymphocytes, plasma cells and eosinophile leucocytes, later on also of fibroblasts. By and by the stroma becomes fibrously transformed while the epithelium will suffer from nutritional disturbances. The chronic catarrh will proceed with acute exacerbations, but will itself persist even if the acute superficial processes decline.

As special forms and further developmental stages of the chronic gastritis Dahl puts down the atrophic-hypertrophic gastritis in which there appear cicatricially thinned, shrunken areas in the thickened mucosa, and the atrophic gastritis in which the whole glandular apparatus disappears and the gastric mucosa assumes a microscopical aspect like an intestinal mucosa with goblet cells and formation of irregular crypts.

The above classification will stand and fall by the correct demarcation between what is normal and what is pathologic. Among ten early fixated, presumably normal, stomachs postmortally removed, Dahl found only three histologically normal ones. Among ten stomachs post-mortally removed Magnus found only two normal. The others not only displayed signs of gastritis, but had also, in small areas, metaplasia to intestinal epithelium, and one was carcinomatous. It is characteristical that certain pathologists have resorted to examinations of infantile and foetal stomachs to obtain normal material at all.

The demarcation will depend upon how much is considered permissible of leucocyte and lymphocyte accumulations in the mucosa. Faber, Konjetzny and others hold forth that the stroma should only contain fibroblasts and smooth muscle cells. Aschoff permits the presence of small amounts of leucocytes, and states that small accumulations of lymphocytes may normally be found. Schreiner mentions lymphocyte follicles as normally present; Stoerk feels that they imply a lymphatic diathesis; whereas Dahl with several other authors, state them to be an inflammatory, symptom. From the above it will appear that the matter may scarcely be regarded as settled as yet. It is, indeed, rather unusual that a feature found in at least 75—80 per cent of healthy individuals should be regarded as pathological, even if it in certain cir-

cumstances may prove to be so, (e.g. dental caries may occur in nearly 100 per cent of the population). But the question must spontaneously arise whether the canalis of the stomach should be regarded, to a certain degree, as a lymphatic organ. It would seem reasonable to expect that the canalis area as a lymphatic organ should react more strongly to irritants than the rest of the gastric mucosa, and that inflammatory phenomena should then be histologically more conspicuous.

During recent years the problem has been attacked by means of gastroscopy. This mode of examination gives us the advantage of studying the appearance of the mucosa in vivo, while the mucosa is capable of function and alterations, and consequently showing a more physiological picture. But the gastroscopy reveals the colour and form of the surface only: from these features we must try to draw conclusions as to the processes going on in the deeper layers, and this is possible only to a certain degree. The gastroscopy gives only a macroscopic picture showing the areas next to the objective somewhat enlarged and the distant areas a bit reduced. This should be born in mind as being of a certain importance when we try to judge the condition of the canalis because the areas near the pylorus will always appear somewhat reduced even when viewed from the most advantageous angle. Best suited for a minute survey is the corpus of the stomach. But it must be remembered that the gastroscopist inspects an inflated, more or less distended stomach. This distension of the stomach is important because at a stronger inflation the signs of a superficial catarrh may disappear. We feel that this feature is also of special importance when we examine the canalis which will always become distended on account of the patient's position during the examination.

By means of gastroscopy we may survey, first and foremost, the degree of reddening present, and, contingently, an uneven distribution of the reddening. Furthermore, we may observe tenacious, adherent mucus, erosions, ulcers, tumors, superficial and submucosal hemorrhages. Finally we take note of the course and thickness of the mucosal folds and whether the mucosa is oedematous and swollen or atrophic.

The reddening is an essential part of the inflammatory process, especially in a mucous membrane: in certain circumstances it may figure as a far more prominent factor than the inflammatory cell

infiltration. As an illustration of the above the milder forms of catarrhal conjunctivites may be mentioned. On the other hand, a comparison of a superficial gastritis with a catarrhal conjunctivites might also throw some light upon a possible source of error in the gastroscopy: — At increased secretion, i.e. weeping, the conjunctiva turns oedematous and red and takes on the same appearance as during a catarrhal inflammation. The gastric mucosa also reddens at increased function, i.e. after a meal. The following question may therefore arise: — Does the superficial catarrh, the change of colour, which is present in most cases of peptic ulcers, imply an irritatively increased function of the gastric mucosa? May perhaps a certain degree of oedema and a slight thickening of the folds be considered in the same way? These questions will later on be more fully discussed.

A histological check of his observations will be of great importance to the gastroscopist. Unfortunately the opportunity for this is restricted as only surgically removed specimen, i.e. the distal part of the stomach, may be microscopically examined. Henning maintains that the histological observations are in keeping with the gastroscopical ones. Magnus and Rodgers also state a good conformity, but Rodgers is probably more cautious in his diagnoses of gastritis than many other gastroscopists. Hancock and his pathologist have gastroscopically and histologically made rather divergent findings. No doubt Hancock's diagnosis of gastritis generally held true, but the pathologist always contested his frequent descriptions of hypertrophy.

As previously mentioned with regard to gastritis the pathologists state that whether an ulcer is present or not, the antrum seems to be the place of predilection of gastritis. Dahl has during his investigations found the gastritis particularly in the same area as the pyloric glands. From this place it may spread upwards into the corpus, but the uppermost parts of corpus and fornix are most often not affected. — The gastroscopist will generally find the symptoms of gastritis to be most pronounced in the lower part of the corpus. Antrum appears to him as a relatively smooth-walled, distended tube, in which folds mainly are present in connexion with the peristalsis. The gastritis in the antrum must be judged chiefly according to the degree of reddening present, and we can therefore best form an opinion with regard to the superficial catarrh.

Certainly, in rare cases a great thickening and contortion of antral folds may be seen.

A question always arising when gastritis is discussed is its relation to the ulcer disease. Konjetzny's hypothesis, that ulcers take their origin in gastric erosions is contested by all gastroscopists except Korbsch; Henning has in his enormous material noted perhaps such an occurrence in one case. But most investigators agree that most often, if there is an ulcer gastritis will also be present, and that some connexion must exist between the two. Henning states that gastritis constantly accompanies the ulcers of the stomach and duodenum. Christiansen found gastritis in 70 per cent of his cases of duodenal ulcer. It should be noted that Christiansen takes a strong ground against the pathologists who insist that gastritis is mainly found in the antrum, and he maintains that the corpus is first and foremost affected, perhaps both corpus and antrum, but never antrum alone. Freeman also stresses corpus as the site of the gastritis. We, ourselves, have made observations similar to Christiansen's, except that we in our material have found gastritis to accompany duodenal ulcer even more frequently than mentioned by him, in other words in practically every case. But we believe that the mode of observation is the explanation of the moderate findings of gastritis in canalis. When the patient during the examination lies on his left side, the canalis will become distended by the ascending air and stretched by the drooping corpus. Furthermore, the canalis will appear reduced because of its distance from the objective lens. And we do not feel entitled to state that the antrum is free of gastritis, as Christiansen does. Henning most often finds hypertrophic gastritis in cases of ulcer, but Christiansen states that a superficial catarrh alone is a more common occurrence than a hypertrophy. In our ulcer patients the gastritis was in nearly half of the cases of the hypertrophic type. As stated by Christiansen it is generally not the heaviest types of hypertrophic gastritis which are found simultaneously with duodenal ulcer, at any rate not when there is no retention.

It may be discussed, as previously mentioned, whether the »gastritis» seen in ulcer patients is not, in reality, only a reddening and perhaps a slight oedema caused by a state of hyperfunction. Is there any connexion between the »gastritis» and the increased acid values of the gastric juice? The acid values do not generally

decrease noticeably during a dietary course apart from what is accounted for by an improved emptying. But often the superficial catarrh decreases during a dietary course (Henning). According to our experiences this especially happens in those patients whose subjective troubles vanish. If, after a dietary course, a new gastroscopy is performed upon ulcer patients with hypertrophy and superficial catarrh, we may often see that the latter has vanished but the former persists in the form of some thickening and irregularity of the folds. Our written description of a case may, for instance, run — «Slightly hypertrophic gastritis in a peaceful phase» — It must be stressed in this connexion, however, that the heavier forms of gastritis do not generally improve on a dietary regimen, but with regard to both superficial catarrh and hypertrophy they will persist rather unchanged in spite of every treatment.

Magnus and Rodgers maintain that they have never seen any case of real mucosal hypertrophy in their material of duodenal ulcer with gastritis. They hold that «état mamellonné» is not due to hypertrophy and that a thickening of the mucosal folds is only a consequence of increased acid production. We do not fully agree in the latter statement, as we have often gastroscopically found hypertrophic folds together with normal acid values: Christiansen has made the same experience.

Forssell and Grettve have ascertained that when a normal stomach is given a digestive task both the course and the size of the mucosal folds are dependent upon the momentary state of function. The aspect of the folds is also affected by drugs which influence the vegetative nervous system. Certain authors use these features as an argument against reading the coarseness of folds as a symptom of gastritis, especially roentgenologically. To this we must answer that at the roentgenological examination the patient is fasting and is not influenced by drugs. The stomach is exposed only to the slight irritament of the mouthful of opaque medium which is given for the mucosal examination, and which is constant in all cases. We must, therefore, be permitted to claim an abnormal course and size of the folds to be a symptom of gastritis, at any rate to such an extent as is empirically confirmed by other methods of examination.

In our cases of duodenal ulcer the gastritis was generally more conspicuous and diffusely spread out than in the cases of gastric

ulcer. In the latter the gastritis was found in patches and it most developed in the neighbourhood of the ulcer. In cases of gastric ulcer the mucosa may obtain a quite normal aspect after a successful dietary course. These features may perhaps be explained by a greater tendency towards a slight retention in cases of duodenal ulcer.

---

The symptomatology of gastritis is very varied and does not help us to define any clinical conception of gastritis, rather quite the contrary. The symptoms are to a certain degree the same for both gastritis and ulcer, and again the question will arise — which is the primary one of these two diseases. Anamnestically we may meet all kinds of pictures, even a subjective symptomlessness; a »syndrome pylorique» like that of ulcer is rather common. All other types of dyspepsia may also occur.

Laboratory examinations give only slight and inconclusive information concerning the gastritis: — the acid values of the gastric juice may vary considerably. Some authors describe a tendency towards increased values, others maintain the opposite, but all agree that both aberrations may occur. In spite of the atrophic areas increased values may be found in stomachs suffering from atrophic-hypertrophic gastritis. Sometimes a quite normal mucosa may be seen gastroscopically in cases of achlorhydria, even though the most common appearance is atrophy. Consequently, the acid values do not allow any definite conclusion to be drawn neither when determined after an Ewald's test meal nor when measured after fractionated aspiration. — Henning attaches some importance to the fact that in cases of gastritis a reduction test of a fractionated test meal generally turns out positive. This phenomenon consists in the more rapid decoloration of methylen blue which has been injected through the tube into the stomach; the gastric contents will again turn colourless because the dye is reduced to its leucobase.

An increased amount of mucus has often been taken to indicate gastritis. When mucus is found to be admixed in an aspirated test meal it should originate from the stomach, whereas floating mucus should come from the pharynx and gullet. Experience will soon teach that this distinction is not a good one. More use will be

derived from examinations of the mucus contained in the gastric juice aspirated from fasting patients.

The aspiration of gastric juice from a fasting patient ought to be performed during fluoroscopy and through a duodenal tube. This is the best way of emptying the stomach, as stated by Bakke. Some content is found in almost every stomach, both the healthy and the diseased. From pathological stomachs we have, both in cases of acid gastritis and of duodenal ulcers, aspirated as much as 130 cm<sup>3</sup> of fluid without any sign of retention of food particles. The amounts aspirated, however, differ very much — from 10 cm<sup>3</sup> up to more than 100 cm<sup>3</sup>, the average being some 50 cm<sup>3</sup>. Similar amounts are found in cases of gastric ulcers, whereas the content in anacid stomachs is small, generally less than 20 cm<sup>3</sup>. All these figures are given on the assumption that there is no retention. We once aspirated 100 cm<sup>3</sup> juice from a gastroscopically and roentgenologically normal stomach during fast, from another 96 cm<sup>3</sup>, but altogether we have aspirated somewhat less from the normal stomachs than from the diseased ones. In 60 per cent of cases the gastric content is more or less gall-stained because of reflux. This feature must be regarded as normal — we have found it in persons gastroscopically healthy quite as often as in the diseased. It certainly does not cause the gastritis. The reactions of the gastric juice from fasting persons also differ considerably; we have obtained higher acid values than after any test meal, but it has also often happened that the juice from fasting persons has been of an acidity lower than the Ewald figures. The acid values of one and the same fasting person may vary considerably from one test to another, more so than the Ewald figures, and the alterations have no law-directed connexion with the state of the gastritis. In cases of acid gastritis the acid values of the fasting juice, measured *ad modum* Ewald have ranged from 0/6 up to 100/120, on an average some 35/45. In cases of duodenal and gastric ulcers the values were very much similar. Free hydrochloric acid was never found in the juice from a fasting person when it was not present after an Ewald's test meal. In gastroscopically and roentgenologically normal stomachs the acid values varied from 0/10 up to 88/94 (the latter patient had Ewald figures 48/68), but they were, on an average, somewhat lower than in cases of gastritis and ulcer. Reflux should decrease the acid values, but the gall-stained gastric juices are



Table I.

Roentgen Diagnosis	Total Number of Patients	Number of patients whose total amount of gastric juice, during fast, contained more mucous sediment than:—			
		2 cm <sup>3</sup>	per cent of cases	3 cm <sup>3</sup>	per cent of cases
Normal stomach .....	100	20	20	10	10
Uncomplicated gastritis ..	52	46	88	36	70
Gastric ulcer:—					
with gastritis .....	18	16	89	13	72
without " .....	1	0		0	
Duodenal ulcer:—					
with gastritis .....	27	23	85	23	85
without " .....	14	4	29	1	7
Gastritis with or without ulcer .....	97	85	88	72	74

often strongly acid. Perhaps some of the slightly acid and colourless juices consist partly of swallowed saliva.

There are several ways to use when trying to determine the amount of mucus in the gastric juice aspirated from a fasting patient. The most simple method is to place the whole of the aspirated portion in a measuring glass for sedimentation. A sediment of mucus together with cell debris and epithelium will then be formed. Often a small amount of foaming mucus will also be seen floating on top of the juice. The amount of sediment formed in 24 hours may offer a certain support for the gastritis diagnosis.

Bang and Holtermann compared the amount of sediment in the gastric juice from 212 fasting patients with the findings at the roentgenological examinations; they found that there was generally a larger sediment in cases of roentgen-diagnosed gastritis (Table I).

The bulk of a mucous sediment, however, depends to a certain degree upon the reaction of the milieu in which it settles. The bulk will increase with a higher pH (decreasing acidity). To avoid measuring the mucus in a swollen state we have therefore performed a series of sedimentations in a milieu of a fairly constant, low pH.

The whole of the gastric juice aspirated from the fasting patient is vigorously shaken. To 10 cm<sup>3</sup> of the juice is added two drops of a 0.04 per cent solution of thymolblue which will change from yellowish brown to a strong red colour if the pH. sinks below 1.5. If no reddening occurs, a 10 per cent hydrochloric acid is added drop by drop until the colour changes. The portion is thereafter diluted with water to 15 cm<sup>3</sup>. After another shaking the glass is put aside for sedimentation for 24 hours. The use of a graduated centrifugeglass with a good distance between the dividing lines in the narrow, lower end is very expedient, but no centrifugation ought to take place.

Unfortunately this test suffers from the same draw-back as the other mucus determinations, i.e. it is influenced by the swallowed secretions from naso-pharynx. Part of the mucus from the upper air passages is certainly dissolved, but scarcely all of it, and especially not the cell debris. The gastric juice from patients suffering from colds always gives an increased amount of sediment. On the one hand, a catarrh in the upper air passages may very often be accompanied by a superficial catarrh of the stomach. In such cases of secondary gastritis the fasting juice will always give plenty sediment, more than the degree of gastritis may account for. On the other hand a fairly abundant sediment may also occur in the gastric juice from persons with a healthy stomach but suffering from a catarrh in the air passages. It must be admitted that the above constitutes a rather heavy objection against using the method, but which of our laboratory methods can give us quantitatively absolute reliable information about the conditions in the stomach?

All in all, quite a good conformity exists between the results of the sedimentation test and the gastroscopical findings. A sediment less than 0.1 cm<sup>3</sup>, i.e. 1 per cent of the amount of gastric juice employed, is very rare in stomachs suffering from a superficial catarrh. 0.1—0.2 cm<sup>3</sup>, i.e. 1—2 per cent, may occur both in a normal and in a diseased stomach, but at sediments larger than 0.2, i.e. 2 per cent, a normal gastric mucosa is very seldom found, — at any rate if it can be excluded that the mucus has been swallowed. The test gives no clue as to whether a superficial catarrh is complicated by hypertrophy or not. A hypertrophic gastritis in a quiet phase may give only a small amount of sediment. The atrophic-hypertrophic



rely placed stomach will normally have a more coarse relief than an ordinary angular stomach (Teschendorf), and the course of the folds in the former may also be somewhat irregular. The diagnosis of a gastritis is, therefore, much more difficult in a »Stierhorn ventrikel« than in an angular stomach, and even more so because the presentation of the mucosal pattern of the squarely placed stomach is generally attended with more technical difficulties. When dealing with this kind of stomachs we are sometimes unable to reach our goal roentgenologically. In this connexion we would just mention that a squarely placed stomach seldom contains any greater amount of secretion, — it would simply be weighed down into an angular form by any larger amount.

In an atonic stomach the folds will often be quite coarse without, therefore, warranting the correctness of a gastritis diagnosis. In these stomachs an irregular course of the folds is rather seldom, even in connexion with gastritis. A roentgenological diagnosis of gastritis may accordingly also in these cases be rendered impossible. There is a fair chance of a correct diagnosis, preferentially when we are dealing with an ordinary angular stomach, and here a positive diagnosis of gastritis will be of real significance.

A gross alteration, which permits the gastritis diagnosis to be made in all kinds of stomachs, is the so-called »Körnchung«, granulation of the mucosal pattern (*état mamellonné*). This state occurs rather seldom. We have the impression that it is seen even more infrequently if a complete aspiration is performed before the examination, and that it should consequently partly be due to mucous secretion in the stomach. This will represent no source of error, however, because a secretion of such a consistency and in such an amount will occur only in connexion with gastritis. The granulation may certainly also be due to mucosal changes proper.

Most investigators assert that one cannot, from abnormally slender mucosal folds derive at any conclusion as to mucosal atrophy: our experience confirms this statement.

The mucosal pattern is easily altered by drugs (Gretlve, and others), and this fact is frequently put forth as an objection against founding a diagnosis of gastritis upon the roentgenological aspect of the pattern. A mucosal pattern quite similar to that of gastritis may be produced in a normal stomach by means of pilocarpin. All the same, one may ask whether such objections are not of more

theoretical than practical value. We believe that a radiologist, trained in the estimation of mucosal patterns, will very seldom diagnose a gastritis which cannot be ascertained gastroscopically. And, besides, the roentgenological examination does not claim to reveal *all* cases of gastritis.

The roentgenological examination cannot tell us the cause of the mucosal swelling which is observed in the single, individual case, whether it is due to a hypertrophy of the submucosa, to oedema of the submucosa and mucosa, or to a state of contraction of muscularis mucosa. All of these three factors may probably play some part but for the present we are unable to tell how much each separate factor has to say. It is probable that the functional state of contraction is of great importance. A superficial catarrh and a hypertrophic gastritis, both of them gastroscopically ascertained, may roentgenologically offer identical aspects. Here again the above-mentioned question will appear, whether the so-called gastritis, is, to some degree, really a functional, or rather dysfunctional, condition. And if a superficial catarrh roentgenologically shows coarse folds, it must be remembered that the roentgenological mucosal pattern is not identical with the relief seen gastroscopically. At the roentgen examination the stomach is empty but for a small amount of contrast medium, — at gastroscopy it is distended by air. A direct comparison is therefore impossible. Even an atrophic gastritis may give coarse folds roentgenologically, but preferably if there is also a superficial catarrh. It must be admitted that the purely superficial catarrhs never give the most monstrously coarse mucosal patterns roentgenologically.

We may in some cases observe gastroscopically how the superficial catarrh of an active, hypertrophic gastritis disappears during a suitable treatment, leaving only a hypertrophic gastritis in an inactive phase behind. Such a change from an active to an inactive phase will not assert itself roentgenologically, — the mucosal pattern will, on the whole, remain the same. The roentgenological examination cannot give any information as to the degree of activity of the process, or whether only sequels of it are left. This feature is probably of importance for the consideration of stomachs operated upon, i.e. gastroenterostomies with or without resection. In connexion with an operation there will appear an inflammatory

Table II.

Roentgenological Diagnosis:—	Gastroscepic Diagnosis of Gastritis:—			
	Super- ficial Catarrh	Hypertrophic & Hypertrophic- Atrophic Gastritis	Atrophic Gastritis	No Gastritis
Nil .....	7 (5)	0	1 (1)	30 (30)
Gastritis .....	60 (48)	65 (39)	8 (7)	7 (7)
Ulcer without gastritis ..	9 (6)	0	0	6 (6)
Duodenal or gastric ulcer and gastritis ....	62 (40)	65 (37)	0	0
Cancer and gastritis ....	0	25 (22)	0	0

The material consists of 248 patients on whom 345 gastroscopies have been performed.

The figures outside the brackets stand for the number of gastroscopies, the figures inside the brackets denote the number of patients. The numbers are scarcely representative for an average material of dyspepsia, as they are ruled by whether the clinicians have deemed a gastroscopy desirable.

infiltration of the stomach wall in the environments of the wound. Even if the infiltration is reduced by and by, a hypertrophy of submucosa will always remain, especially around the anastomosis. Roentgenologically coarse mucosal folds will always be seen in these cases. Gastroscepically a hypertrophic gastritis is always found in a stomach operated upon, but how much of the hypertrophy is a sequel of the operation and how much is due to a later gastritis, it cannot be decided. »Active phase», i.e. superficial catarrh, must nearly always be added in the diagnosis, because a mucosa of a normal rose hue is of very rare occurrence in stomachs operated upon.

The conclusion may, consequently, be drawn that a roentgenological diagnosis of gastritis most often implies that the mucosa is pathologically changed; this will appear from our comparison of roentgenological and gastroscepic findings (Table II). But, as several authors have already pointed out, it is not permissible to try roentgenologically to make the more specified diagnosis — hypertrophic gastritis versus superficial catarrh — or to recognise atrophy.

type shows no special distinction. An atrophic gastritis may perhaps give an increased sediment even if there is no superficial catarrh, but our material is too restricted to allow any statement on this point. The above conclusions are based upon sedimentation tests in 56 cases of acid and 5 cases of anacid gastritis, 40 duodenal and 6 gastric ulcers, and finally 28 normal stomachs — altogether 135 cases.

We may easily calculate how much mucous sediment the whole of the aspirated juice should give. As already mentioned the amount aspirated varies much, but under pathological conditions it is, on an average, larger than under normal conditions. The sediment calculated for the whole of the aspirated amount will also be larger for the pathological stomachs, and this is in conformity with the results obtained by Bang and Holtermann; but the absolute figures calculated for the total amount will show a wider dispersion than the percentage figures. The border between pathological and physiological conditions will be more diffuse.

Various investigators have made many attempts to determine the amount of mucus also by chemical analyses, not only by the simple sedimentation tests. These methods, however, will also be subject to possible errors caused by swallowed respiratory mucus. Beside cells and debris the gastric secretion contains mucin (a glucoproteid) as well as dissolved protein. The protein cannot be precipitated separately, because the mucin acts as a protective colloid (Baltzer). Both the protein and the mucin are reductive agents, but the mucin is much more so than the protein. Anreep and others have measured the reductive power after acid hydrolysis, i. e. for the mucin and the protein together. Baltzer precipitates the mucin plus 50 per cent of the protein by means of acetone and sulfosalicylic acid; he thereafter dissolves the precipitate and determines its reductive power *ad modum* Hagedorn-Jensen. He feels that this latter method is by far the best when he wants to determine the amount of mucin. All the reduction methods are rather too laborious for clinical use. The joint determination of protein and mucin may probably be of some importance for the diagnosis of the mucosal inflammation, the gastritis, as it is likely that there would be an increase of both protein and mucin in such cases. To gain some experience on these matters we have made a series of nitrogen-determinations (micro-Kjeldahl) in gastric juice from fasting

(Aus dem Långbro sjukhus, Älvsjö-Stockholm; Chef: Docent med. dr. S. Stenberg).

## Über gerinnungsaktive Stoffe in der Zerebrospinalflüssigkeit.

I. Mitteilung.

Von

Professor V. KAFKA.

(Bei der Redaktion am 16. Juni 1944 eingegangen).

Über die Einwirkung der Zerebrospinalflüssigkeit (Zsp.) auf den Vorgang der Blutgerinnung ist wenig bekannt. Zwar wissen wir, dass bei experimenteller und artefizieller Blutbeimengung zur Zsp. die Blutgerinnung (Ger.) fast ebenso verläuft wie in einer indifferenten Flüssigkeit z. B. physiologischer Kochsalzlösung, mit dem einzigen Unterschied, dass die Retraktion des Koagulums etwas schneller vor sich zu gehen scheint. Daraus ist nur zu schließen, dass sich in der Zsp. kein Antithrombin findet. Ferner wissen wir, dass bei starker Erhöhung der Permeabilität z. B. beim Stauungsliquor Ger. aktive Stoffe und auch das Fibrinogen aus dem Blute in die Zsp. übergehen können, und es infolgedessen zu spontanen Ger. vorgängen kommt (coagulation massive). Etwas Ähnliches nur in anderer Form findet bei den akuten infektiösen Meningitiden statt. Welche Einwirkungen aber die normale Zsp. und auch jene bei Erkrankungen, die nur mit relativ geringer Permeabilitätserhöhung (wie z. B. die Paralyse) oder ohne eine solche einhergehen, auf die einzelnen Ger. faktoren hat, ist so gut wie unbekannt. Ich selbst habe vor vielen Jahren auf Grund einiger orientierender Versuche die Meinung geäußert, die Zsp. enthielte Fibrinferment (30). L. Neufeld (39) war der Meinung, dass die



Goldsolreaktion der Zsp. eine Thrombin-Antithrombinreaktion darstelle; er hat aber nie den direkten Nachweis des Thrombins oder Antithrombins in der Zsp. versucht, sondern Analogieschlüsse gezogen, so dass seine Feststellungen nicht den wirklichen Verhältnissen entsprechen.

Die Aufgabe, die wir uns stellten, war also, die Zsp. von Normalen und von Fällen ohne gröbere Störung der meningealen Permeabilität auf ihr Verhalten den einzelnen Komponenten des Ger. prozesses gegenüber zu untersuchen. Auf Grund der vielen Arbeiten, die in den letzten Jahren über die Ger. geschrieben worden sind, stand uns hier eine grosse Reihe von Methoden zur Verfügung, wenngleich wir uns von vornherein darüber klar waren, dass die theoretischen Grundlagen zum Teil noch weit von einer vollständigen Klärung entfernt sind. Wir werden am Schlusse der Arbeit auch auf diese Punkte eingehen.

### *I. Allgemeine Methodik.*

Da die Technik den einzelnen Versuchen und Fragestellungen angepasst werden musste, wird Spezielles darüber bei den einzelnen Versuchsanordnungen zu sagen sein. Hier sei nur die allgemeine Methodik besprochen. Wir mussten natürlich von einer geeigneten Fibrinogenlösung ausgehen. Als solche standen uns die verschiedenen Plasmen, vor allem Zitrat-, Oxalat- und Magnesiumsulfatplasma, zur Verfügung. Wir gingen vom Magnesiumsulfatplasma aus. Es wurde nach Wohlgemuth in der Weise hergestellt, dass wir zu 1 cm<sup>3</sup> 28 % iger Magnesiumsulfatlösung 3 cm<sup>3</sup> Venenblut im Strahle hinzutreten liessen. Wir blieben bei dieser Magnesiumsulfatkonzentration, trotzdem Fonio eine 14 %ige Lösung empfiehlt und von diesem Autor zu Versuchen mit kurzer Ger. zeit auch ganz niedrige Konzentrationen angewendet werden. Nach Mischung wurde sofort scharf zentrifugiert. Bezüglich der Zentrifugierzeit sei hervorgehoben, dass wir zuerst nur 10 Min. (Dyckerhoff und Mitarbeiter) zentrifugierten, später aber wurde diese Zeit auf eine Stunde ausgedehnt, um das Blutplasma plättchenfrei zu bekommen. Lesourd und Pagniez (35) betonen zwar, dass plättchenfrei zentrifugiertes Plasma langsamer gerinnt als kurz zentrifugiertes. Eigene Versuche mit Oxalatplasma, das 10 und 55' zentrifugiert worden war, zeigten bei 37 Grad nur

eine Differenz von 0.5' bez. der Ger. zeit. Deshalb und weil wir das Vorhandensein der Plättchen im Plasma für eine Fehlerquelle halten, die bei der Deutung der Ergebnisse Schwierigkeiten machen kann, zentrifugierten wir immer lange und scharf. Um einen Überblick über die Menge des im Versuch zu verwendenden Plasmas zu haben, setzten wir den alten Wohlgemuthschen Versuch an, der darin besteht, dass man zu absteigenden Mengen von Magnesiumsulfatplasma, die mit 1 %iger Kochsalzlösung auf das gleiche Volum aufgefüllt werden, je 1 cm<sup>3</sup> 5fach verdünntes frisches Normalserum hinzusetzt. Nach 24 stündigem Aufenthalt im Eisschrank liest man ab. Wohlgemuth hat diese Methode zur Ermittlung der Fibrinogengehaltes der Plasmas angegeben. Für diesen Zweck scheint sie uns jedoch nicht ganz einwandfrei, denn wir erhielten ein Optimum der Ger. bei 0.25 cm<sup>3</sup> Plasma. Ein Gleiches stellten Wöhlisch und Juhling (51) sowie Wöhlisch, Diebold und Kiderlen (52) fest. Über diesen Punkt, die Konzentration des Fibrinogens in den Plasmen, die von den meisten Autoren vernachlässigt wird, wird noch a. a. St. zu sprechen sein. Hier sei nur bemerkt, dass wir in Übereinstimmung mit Wöhlisch, Diebold und Kiderlen (52) die kürzeste Ger.zeit bei normalen Fibrinogenmengen (ca 200 mg %) gesehen haben. Wir sind auf den oben genannten Versuch nicht mehr zurückgekommen, zumal sich empirisch herausgestellt hatte, dass mit 0.1 cm<sup>3</sup>, ja auch 0.05 cm<sup>3</sup> Plasma gute Resultate zu erzielen waren. Zitratplasma wurde in der bekannten Weise hergestellt, bezüglich des Oxalatplasmas bedienten wir uns der Angaben von Dyckerhoff (16) sowie Kürten und Harzer (32). Wir verwendeten aber nicht Ammoniumoxalat sondern Natriumoxalat u.zw. setzten wir zu 1 cm<sup>3</sup> der 2 %igen Natriumoxatlösung 9 cm<sup>3</sup> Blut. Manche Autoren empfehlen eine Verdünnung des Plasmas mit Wasser vor seiner Verwendung. So gibt Wöhlisch an, man solle das Magnesiumsulfatplasma auf das 3—8fache mit Wasser verdünnen und Dyckerhoff, Behn, Goossens und Michler (15) sowie Kürten und Harzer (32) schlagen eine 5fache Verdünnung des Oxalatplasmas mit Wasser vor. Die ersten Autoren meinten, man könne mit dem mit Wasser verdünnten Oxalatplasma genauer das erste Auftreten der Gerinnung beobachten. Hans J. Fuchs (21) beobachtete schnellere Gerinnung bei Verdünnung des Plasmas mit Wasser. Wir haben solche Erfahrungen nicht gemacht. Orientierende Versuche zeigten uns kaum Gerinnungsdifferenzen zwi-

sehen verdünntem und unverdünntem Plasma, bei letzterem aber war meist totale Gerinnung zu beobachten, während sie bei erstem oft partiell blieb. Bezüglich des Magnesiumplasmas sei gesagt, dass wir die Wasserverdünnung in den meisten Versuchen absichtlich unterlassen haben, weil durch die starke Salzkonzentration die Wirkung des Prothrombins gehemmt wird, eine Erscheinung, die, wie wir sehen werden bei den Versuchen mit Zsp. oft erwünscht ist.

Um die einzelnen Gerinnungsfaktoren ermitteln zu können, haben wir uns Thrombokinese und die geeignete Calciumchloridlösung hergestellt. Die Thrombokinese wurde nach Quick (40) und Lehmann (33, 34) aus menschlicher Gehirnrinde hergestellt. Dabei wurden die Vorschriften befolgt, wie sie Boström in ihrem Buche gibt. Dies gilt auch bezüglich der 0.5 %igen Calciumchloridlösung nach Lehmann (l. c.) Für einige Versuche haben wir uns auch einer nach Lehmann (l. c.) fabrikmässig (Ferrosan-Fabrik) hergestellten Calciumchloridlösung (0.334 %ig) und eines ebensolchen Thrombokinesepräparates bedient. Als Ergänzungsflüssigkeit wurde in den Versuchen zuerst 1.0 später 0.9 %ige Kochsalzlösung verwendet. Mit Kürten und Harzer (32) stimme ich darin überein, dass das Versuchsergebnis durch grössere oder kleinere Mengen der Verdünnungsflüssigkeit nicht wesentlich verändert wird.

Wir liessen die Magnesiumsulfatversuche zuerst alle im Eisschrank ablaufen und liessen nach 24 Stunden ab. Dabei versuchten wir, die Grösse des Gerinnsels abzuschätzen. Hierbei kam uns ein Kunstgriff sehr zugute, der darin bestand, dass wir zu den Röhrchen verdünnte Methylenblaulösung hinzusetzten nzw. 0.1—0.2 cm<sup>3</sup> pro cm<sup>3</sup> der Flüssigkeit. Wir haben dann folgende Grade der Grösse des Gerinnsels bezeichnet: (((+))), ((+)), (+), +, ++, +++ und +++++. Bei weiteren Versuchen bedienten wir uns natürlich der Zimmer- und höherer Temperaturen. Hier wurde die Gerinnungszeit bestimmt, also jene Zeit, die mit der Fertigstellung des Versuches beginnt und mit dem Auftreten der ersten Gerinnungsercheinungen endigt. Als Kontrolle für die Besonderheit des verwendeten Plasmas müssen jedem Versuch beigegeben werden: eine Probe mit der optimalen Calciumchloridmenge + Plasma und zweitens Plasma + Kochsalzlösung, letztere deshalb, weil sie zeigt, ob im Plasma keine Spontanflockung aufgetreten ist. Darüber hinaus gilt selbstverständlich die Forderung, dass alle ange-

wendeten Flüssigkeiten vollkommen frei von Flocken und Trübungen sind; im anderen Fall müssen sie klar zentrifugiert werden.

Bei der Untersuchung der Zsp. erfolgt selbstverständlich nebenbei eine genaue anderweitige Prüfung, vor allem wurde auch mit Hilfe der Eiweissrelation (Kafka) der Gesamteiweiss-, Globulin- und Albumingehalt bestimmt.

## II. Versuche mit Magnesiumsulfatplasma.

Wir wollen zuerst über Versuche mit *Magnesiumsulfatplasma* bei Eisschranktemperatur berichten, weil es sich gezeigt hat, dass der Ger. prozess bei Eisschranktemperatur und Verwendung von Magnesiumsulfatplasma am langsamsten abläuft, sodass die Hauptablesung nach 24 Stunden geschehen, und die Stärke der Gerinnung nach der Grösse des Gerinnsels beurteilt werden kann. Da sämtliche Recalcifizierungsversuche des Plasmas unter diesen Bedingungen negativ ausfallen [vgl. auch Wöhlisch (49, 50)], werden sie in den Tabellen nicht angeführt. Diese Erscheinung ist als ein Vorteil anzusehen, weil eine auftretende Ger. nicht allein auf Bestandteile des Plasmas besonders ihre Thrombokinasen zurückgeführt werden kann. Es sei aber gegenüber Wöhlisch angeführt, dass die Recalcifizierung des Magnesiumsulfatplasmas bei Zimmertemperatur jederzeit gelingt. Wir wollen nun eine Reihe von Versuchen an uns vorüberziehen lassen. Der erste Versuch (Pr. Nr. 4, Tabelle 1) zeigt uns, dass 1 cm<sup>3</sup> Zsp. nicht befähigt ist, die Ger. von 0.2 cm<sup>3</sup> Magnesiumplasma im Eisschrank zu aktivieren, während ein Normalserum u.zw. 0.2 cm<sup>3</sup> auf 1 cm<sup>3</sup> verdünnt deutliche

Tabelle 1.

Einwirkung von 1.0 cm<sup>3</sup> Zsp. auf MgSO<sub>4</sub> Plasma im Eisschrank.

Eisschrank	Liq. Sö.	Liq. Mo.	Liq. Ahl.	Liq. Cl.	Liq. Hedv. + Liq. Pett.	Sc. Ma 1/5	K
Liquor oder Serum . . . .	1.0	1.0	1.0	1.0	0.6	1.0	.
1 %ige NaCl Lös. . . . .	0.8	0.8	0.8	0.8	1.2	0.8	1.8
MgSO <sub>4</sub> Plasma . . . . .	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Ergebnis nach 24 Stunden	0	0	0	0	0		0

0 = Keine Ger. innerhalb der Versuchszeit

Tabelle 2.  
Trypsinaktivierung.  $MgSO_4$  Plasma. Eisschrank.

Eisschrank	Liq. Ol.	Liq. Ol.	Liq. Gi.	Liq. Gi.	Liq. Olof.	Liq. Olof	K
Liquor o. Serum . . . .	1.0	1.0	1.0	0.8	1.0	1.0	—
1 %ige NaCl Lös. . . . .	0.1	—	0.1	0.2	0.1	—	1.0
Trypsinlösung . . . . .	—	0.1	—	0.1	—	0.1	0.1
$MgSO_4$ Plasma Ka . . . .	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Ergebnis nach 24 St. . .	$\theta$	$\theta$	$\theta$	$\theta$	$\theta$	$\theta$	$\theta$

$\theta$  = Keine Ger. innerhalb der Versuchszeit.

Tabelle 3.

Aktivierung von 1.0 cm<sup>3</sup> Zsp. durch Thrombokinase oder  $CaCl_2$  ( $MgSO_4$  Pl. Eisschr.)

Eisschrank	Liq. Ha.	Liq. Ha.	Liq. Ha.	Liq. Ka.	Liq. Ka.	Liq. Ka.	Se. K. 1/5	Se. K. 1/5	Se. K. 1/5	K.	K <sub>2</sub>
Liquor o. Serum . .	0.1	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	—	—
Trombokinase . . . .	—	0.1	—	—	0.1	—	—	0.1	—	0.1	—
0.5 % $CaCl_2$ L. . .	—	—	0.1	—	—	0.1	—	—	0.1	—	0.1
1 %ige NaCl. L. . .	0.1	—	—	0.1	—	—	0.1	—	—	1.0	1.0
$MgSO_4$ Plasma K. . .	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Ergebnis nach 24 St. . . . .	$\theta$	$\theta$	$\theta$	$\theta$	$\theta$	$\theta$	++	++	++	$\theta$	$\theta$

$\theta$  = Keine Ger. innerhalb der Versuchszeit.

Ger. erzeugt. Über die Diagnose der verschiedenen Fälle der Tabelle sei erst später die Rede, es sei nur hervorgehoben, dass der 5. Fall, bei dem nur 0.6 cm<sup>3</sup> eines Mischliquors verwendet wurden, von 2 Paralysefällen stammt. Hier schien doch wohl eine Spur von Ger. angedeutet. Im nächsten Versuch (Pr. Nr. 5, Tabelle 2) versuchten wir die Ger. nach dem Vorgang verschiedener amerikanischer Autoren [Douglas und Colebrook, Heard, Waldschmitz-Leitz, Eagle (17), Mellanby und Pratt (37)] durch *Trypsin* zu aktivieren. Die Trypsinlösung wurde in der Weise hergestellt, dass 0.2 g Trypsin unter Hinzufügung von 0.1 cm<sup>3</sup> n-NaOH in 60 cm<sup>3</sup> destillierten Wassers gelöst wurden. Einzelheiten sind aus der Tabelle zu sehen, die im Übrigen zeigt, dass eine Trypsinaktivierung bei dieser

Tabelle 4.

 Antithrombin i.d. Zsp. (MgSO<sub>4</sub> Plasma, Elsschrank).

Elsschrank	Liq. Ha.	Liq. Ha.	Liq. Ka.	Liq. Kn.	Se. Ka. $\frac{1}{3}$	K
Liquor o. Serum .....	1.0	1.0	2.0	1.0	1.0.	—
Serum Ka. ....	—	1.0	—	1.0	—	—
Thromboknase .....	—	—	—	—	—	0.1
0.5 %ige CaCl <sub>2</sub> L. ....	—	—	—	—	—	0.1
1 %ige NaCl L. ....	1.0	—	—	—	1.0	1.8
MgSO <sub>4</sub> Plasma Ka. ....	0.2	0.2	0.2	0.2	0.2	0.2
Ergebnis nach 24 St. ....	0	—	((+))	+	—	—

0 = Keine Ger. innerhalb der Versuchszeit.

Versuchsanordnung nicht stattfindet. Im nächsten Versuch (Pr. Nr. 6, Tab. 3) wurde die Frage zu beantworten gesucht, ob 1 cm<sup>3</sup> Zsp. durch 0.1 cm<sup>3</sup> Thromboknase oder 0.1 cm<sup>3</sup> der CaCl<sub>2</sub>-Lösung zur Ger. aktiviert werden kann. Der Versuch zeigt, dass eine solche Aktivierung der Ger. *unter den gegebenen Bedingungen* nicht stattfand, während ein Normalserum in seiner Ger. aktivität nicht verändert wurde. Da die Verhältnisse bei Verwendung von Oxalatplasma anders liegen, wird später noch auf diese Dinge eingegangen werden. Im nächsten Versuch (Pr. Nr. 7, Tabelle 4) sollte festgestellt werden, ob die anscheinend nicht vorhandene Ger. aktivität von 1 cm<sup>3</sup> Zsp. durch ein *Antithrombin* hervorgerufen wird. Das war zwar nach unseren oben erwähnten Erfahrungen bei Zusatz von Blut zur Zsp. nicht anzunehmen, doch war eine experimentelle Klärung notwendig. Es wurde also zu je 1 cm<sup>3</sup> Zsp. einmal Kochsalzlösung und das andere Mal 1 cm<sup>3</sup> verdünntes Serum zugesetzt. Ausserdem wurde Serum ohne Zsp. angesetzt. Es zeigte sich nun, dass das Serum genau die gleich starke Gerinnung hervorrief, gleichgültig ob Zsp. zugesetzt war oder nicht. Unter diesen Bedingungen war also eine antithrombische Wirkung der Zsp. nicht anzunehmen. Es sei hier gleich vorausgeschickt, dass bei Verwendung von Oxalatplasma und Brutschranktemperatur frisches Serum auf die Zsp. stark gerinnungsbeschleunigend wirkt (und umgekehrt), altes Serum jedoch die Ger. aktivität der Zsp. herabsetzt. (Pr. Nr. 151, 153, 154). In dem oben erwähnten Versuch wurden auch 2 cm<sup>3</sup> Zsp. angesetzt. Hier war eine Spur Ger. fest-

Tabelle 5.

Ergebnisse mit  $\text{MgSO}_4$  Plasma bei *Eisschranktemp.*

Name	Datum		Liq.- menge	Ergeb- nis n. 24 St.	Eiweissrelation				Diagnose
	Ent- nahm.	Ver- such			Tot. Prot.	Glob.	Alb.	E. Q.	
Sö.	29—3	6—4	1.0	0	1.3	0.3	1.0	0.33	Epilepsie
Mo.	18—3	6—4	1.0	0	1.4	0.4	1.0	0.4	Lues + Psychose
Aht.		6—4	1.0	0					Paral. mal. beh.
Gi.	12—3	6—4	1.0	0					Paral.
Hedy.	12—3	6—4	0.6	0					Paral.
Pett.	18—3	6—4			2.5	2.0	0.5	4.0	Lues + Ps.
Fors.	30—4	13—5	3.0	0	1.3	0.35	0.95	0.36	Arter. cer.
Ro.	28—4	13—5	3.0	0	1.45	0.55	0.9	0.61	Org. Nervkr.
Ma.	27—4	13—5	3.0	0	1.8	0.5	1.3	0.38	Arter. cer.
We.	9—4	24—4	1.0	0	3.0	0.8	2.2	0.36	
			2.0	0					
Ad.	14—4	24—4	1.0	0	1.9	0.65	1.25	0.52	Arter. cer.
			2.0	((+))					
Olofs.	11—2	26—4	1.5	0					Paral. beh.
Pu.	12—3	26—4	1.5	0					Psychop.
Ham.	19—4	21—4	1.0	0	2.1	0.5	1.6	0.31	Del. tr? Org.
Kam.	16—4	21—4	1.0	0	1.5	0.4	1.1	0.36	Org. Paral.?
		22—4	2.0	((+))					
Lu.	20—5	21—5	1.0	0	2.3	1.3	1.0	1.3	Paral. beh.
		22—5	2.0	0					
Lö.	20—5	21—5	1.0	0	1.5	1.0	0.5	2.0	Paral. beh.
		22—5	2.0	0					
		22—5	3.0	((+))					
		24—5	6.0	f(+)					
Högl.	18—5	19—5	2.5	0	1.95	0.5	1.45	0.33	Org. + Psych
Åker.	22—5	24—5	1.0	((+))	5.0	1.7	3.3	0.51	Paral. atyp.
			2.0	(+)					unbeh.
			7.0	++					
Norm.					0.8 bis 1.3	0.1 bis 0.3	0.6 bis 1.0	0.1 bis 0.4	

0 = Keine Ger. innerhalb der Versuchszeit.

zustellen. Die Zsp. entstammte einer behandelten Paralyse. Auf Grund dieses Ergebnisses setzten wir im folgenden Versuche (Pr. Nr. 8) zwei Zsp. in der Menge von 1 und 2  $\text{cm}^3$  an. In dem einen Fall erhielten wie eine Spur Ger. Es handelte sich hier um eine arteriosklerotische Demenz mit erhöhtem Eiweissgehalt in der

Zsp. Nachdem wir im nächsten Versuch (Pr. Nr. 9) mit 1.5 cm<sup>3</sup> Zsp. keine Ger. erhalten hatten, setzte wir im darauffolgenden Experiment (Pr. Nr. 10) noch *höhere Liquormengen* an und stellten uns zugleich die Frage, ob bei diesen grösseren Mengen durch CaCl<sub>2</sub> eine Ger. aktiviert oder eine vorhandene verstärkt werden kann. Während alle Zsp. in der Menge von 3 cm<sup>3</sup> Ger. inaktiv waren, liessen sich die Fälle Ma. und Ro. bei 3 cm<sup>3</sup> mit CaCl<sub>2</sub> in geringen Masse zur Gerinnung aktivieren. Es sei nochmals hervorgehoben, dass die Kontrolle mit der optimalen CaCl<sub>2</sub> Menge allein negativ verlief. Bevor wir auf diesen Befund näher eingehen, wird in den nächsten Versuchen festzustellen versucht, bei welcher Menge, welcher Diagnose und welchen Eiweissverhältnissen die Zsp. unter diesen Bedingungen Ger. aktiv werden (Tab. 5). Besonders interessant sind hier die Fälle Lu., Lö. und Ak. Der erste Fall zeigt bei 2 cm<sup>3</sup> schon eine fragliche Spur Ger., die freilich bei 1.0 cm<sup>3</sup> negativ ist. Der Fall Lö. zeigt ein ähnliches Verhalten: die Ger. scheint bei 2 cm<sup>3</sup> zu beginnen, ist bei 3 cm<sup>3</sup> deutlich und bei 6 cm<sup>3</sup> noch stärker. Der Fall Ak. reagiert am stärksten: die Ger. ist bei 1.0 cm<sup>3</sup> deutlich, bei 2.0 cm<sup>3</sup> stärker und bei 7 cm<sup>3</sup> kurze Zeit nach Zusatz ++. Interessanterweise handelte es sich bei allen diesen Fällen um Paralysen. Ausserdem zeigte noch ein Mischliquor von 2 Paralysen in der Menge von 0.6 einen Ger. befund?θ, ferner eine fragliche

Tabelle 6.

MgSO<sub>4</sub> Plasma. Eitsschrank. CaCl<sub>2</sub> Aktivierung.

Name	Datum		Liquor- menge	0.5 % CaCl <sub>2</sub>	Ergeb- nis nach 24 St.	ohne CaCl <sub>2</sub>	
	Ent- nahme	Ver- such					
Ham.	19—1	21—1	1.0	1.0	0	0	} CaCl <sub>2</sub> Kontr. 0
Kam.	16—4	21—1	1.0	0.1	0	0	
Fors.	30—1	13—5	2.0	0.1	0	3.0 0	
Ro.	28—1	13—5	3.0	0.1	«+»	0	} CaCl <sub>2</sub> Kontr. 0
Ma.	27—4	13—5	3.0	0.18	(÷)	0	
Hügl.	18—5	19—5	2.5	0.1	0	0	
Lu.	20—5	21—5	1.0	0.1	«+»	0	} CaCl <sub>2</sub> Kontr. 0
		22—5	2.0	0.1	«! »	? 0	
		21—5	1.0	0.1	0	0	
Lö	20—5	22—5	2.0	0.1	(+)	? 0	

θ = Keine Ger. innerhalb der Versuchszeit



Paralyse bei 2.0 cm<sup>3</sup> ((+)). Den gleichen Befund wies die Zsp. einer Arteriosklerose mit erhöhtem Eiweissbefund auf. Bezüglich der Beziehung zur Eiweissrelation überhaupt wäre zu sagen, dass alle Ger. aktiven Fälle einen erhöhten Eiweissgehalt haben, dass aber eine Reihe von Fällen mit erhöhtem Eiweissgehalt Ger. inaktiv ist. Über die schon erwähnte Aktivierung mit CaCl<sub>2</sub> gibt Tab. 6 Auskunft. Ausser den schon erwähnten Fällen Ro. und Ma. werden auch die Zsp. Lu. und Lö. deutlich aktiviert. Diese Tatsache, dass sich Zsp. unter den gegebenen Verhältnissen durch CaCl<sub>2</sub> entweder aktivieren oder bez. der Ger. verstärken lassen, spricht dafür dass eine ev. in der Zsp. vorhandene Thrombokinase zu der im Plasma befindlichen addiert und dann bei Verstärkung des normalen Ca-Gehaltes der Zsp. durch das hinzugefügte CaCl<sub>2</sub> Ger. hervorruft, während die CaCl<sub>2</sub> Kontrolle unter den gegebenen Verhältnissen entweder über nicht genug Thrombokinase verfügt oder die Ca-Menge hier nicht genügend ist. Wir haben aber hervorgehoben, dass die Recalcifizierungsversuche bei jeder CaCl<sub>2</sub> Menge gerinnungsinaktiv bleiben, so dass diese letztere Annahme nicht stichhaltig ist. — Mit der obenerwähnten Zsp. Ak. wurde ein kleiner Versuch, der theoretisch nicht unwichtig ist, ausgeführt. Nachdem wir mit 2 cm<sup>3</sup> Ger. erhalten hatten, entfernten wir das Gerinnsel und setzten den Lignor noch einmal mit Magnesiumsulfatplasma zum Versuch an. Wir konnten keine Ger. feststellen, wodurch wahrscheinlich wurde, dass die Ger. aktiven Stoffe der Zsp. durch den Ger.prozess erschöpft erschienen. Dass das Ergebnis dieses Versuches nicht etwa ein zufälliges war, konnten wir mit Oxalatplasma beweisen (Pr. Nr. 79). Setzt man nämlich 1.0 cm<sup>3</sup> Zsp. mit Oxalatplasma und die zugehörige Kontrolle mit CaCl<sub>2</sub> an, die beide nach 24 St. Zimmertemperatur deutliche Ger. zeigen, entfernt dann die beiden Gerinnsel und setzt neues Oxalatplasma zu, dann gerinnt nur die Recalcifizierungsprobe, nicht aber das Zsp. Röhrchen. Dieser Versuch ist nicht leicht zu deuten, er beweist jedenfalls, dass der Ca-Gehalt der Zsp. für die Ger. nicht allein massgebend war.

Hervor wir auf die weiteren Versuche eingehen, möchten wir die bisher erwähnten Ergebnisse *zusammenfassen*. Bei Anwendung normalen Magnesiumsulfatplasmas und Eisstranktemperatur liess sich in der Zsp. bei 1.0 cm<sup>3</sup> keine Ger. aktivität nachweisen. Nur ein Fall, eine Paralyse mit hohem Eiweissgehalt in der Zsp., bil-

dete eine Ausnahme. Auch durch Zusatz von Trypsin, Thrombo-  
 kinase oder  $\text{CaCl}_2$ -Lösung liess sich bei 1  $\text{cm}^3$  Zsp. keine Ger. aktivi-  
 ren. Eine Ausnahme bildete die Zsp. einer Paralyse, bei der schon  
 bei 1.0  $\text{cm}^3$  eine Ger. aktivierung durch  $\text{CaCl}_2$  gelang. Bei den Men-  
 gen von 2.0  $\text{cm}^3$  zeigten die Zsp. von Paralysefällen eine mehr  
 oder weniger starke partielle Ger., die aber bei höheren Mengen  
 sehr deutlich wurde. Eine Gehirnarteriosklerose mit erhöhtem Ei-  
 weissgehalt in der Zsp. zeigte bei einer Menge von 2.0  $\text{cm}^3$  eine  
 Spur Ger. Alle anderen sicheren Fälle von Nichtparalyse waren bis  
 zur Menge von 3.0  $\text{cm}^3$  Ger. inaktiv. Aktivierung durch  $\text{CaCl}_2$

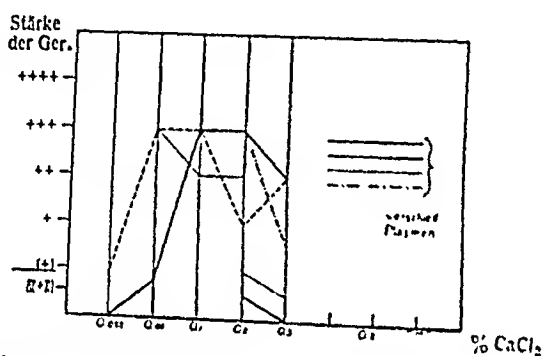


Abb. 1. Recalcifizierung von  $\text{MgSO}_4$  Plasma bei Zimmertemp. nach 24 St.

gelang, wenn auch selten, bei Nichtparalysen bei 2 und 3  $\text{cm}^3$ .  
 Eine Diskussion der Ergebnisse wird später erfolgen. Versuche  
 mit *Zitralplasma* zeigten keine Besonderheiten. *Hirudinplasma*  
 zeigte sich für unsere Versuche ungeeignet, da es auch durch Nor-  
 malserum nicht zur Ger. zu bringen war.

Die weiteren Versuche mit *Magnesiumsulfatplasma*, die bei  
*Zimmertemperatur* erfolgten, müssen gesondert besprochen werden.  
 Hier ist schon wesentlich, dass die Recalcifizierungsversuche stets  
 positiv ausfallen. Die im Plasma enthaltenen Mengen von Ger.  
 faktoren genügen bei dieser Versuchsanordnung, um Ger. hervor-  
 zurufen. Bei diesen Versuchen konnten wir die schon von Wöhlisch  
 (49), H. C. Gram, Kürten und Harzer (32), Lehmann (33, 34)  
 u. a. erwähnte Beobachtung bestätigen, dass für jedes Plasma ein  
 Optimum der Calciumwirkung vorhanden ist, und höhere Mengen  
 die Ger. sogar hemmen können. Diese Verhältnisse sind in Abb. 1  
 deutlich ersichtlich.

Tabelle 7.

Ergebnisse mit  $\text{MgSO}_4$  Plasma bei Zimmertemperatur.

Name	Datum		Liquor- menge	Ergebnis n. 24. St.	Eiweissrelation				Bemerk.	Diagnose
	Ent- nahme	Ver- such			Tot. prot.	Glob.	Alb.	EQ		
Th.	11—6	16—6	0.7	$\theta$	1.2	0.3	0.9	0.33		Enceph. traum.
		15—6	1.0	$\theta$						
		12—6	3.0	++						
Ho.	9—6	16—6	0.91	$\theta$	1.1	0.2	0.9	0.22	Eisschr. 1.0	Epil.
		15—6	1.0	$\theta$						
Ha.	9—6	15—6	1.0	$\theta$	1.2	0.3	0.9	0.33	1.0 $\theta$	Epil.
		16—6	1.5	$\theta$						
Sö.	17—6	23—6	2.5	$\theta$	2.3	0.5	1.8	0.28		Arterioscl. cer.
			3.0	+						
Ho.	17—6	18—6	1.0	$\theta$	2.0	1.2	0.8	1.5		Paral. beh.
Ny.	21—6	21—6	3.0	(+)	1.0	0.3	0.7	0.42		Psychop.
A. And.	25—6	25—6	3.5	((+)))	0.9	0.3	0.6	0.5	Cyst. L.	?
			5.0	$\theta$						
Car.	25—6	28—6	2.5	((+))	1.3	0.35	0.95	0.36		Melanch.
T. And.	30—6	1—7	3.1	+++	1.3	0.3	1.0	0.33		Encephalopath. traum.
Ber.	5—7	5—7	2.0	(+)	2.0	0.65	1.35	0.18		Lues cer.
Ma.	5—7	6—7	1.5	$\theta$	2.0	0.4	1.6	0.25		Org.
			3.0	((+)))						
Fra.	5—7	6—7	3.0	(+)	1.2	0.2	1.0	0.2		Encephal. traum.
Hedv.	9—7	9—7	2.35	(+)	2.3	1.1	1.2	0.91		alte Paral.
Ab.	10—7	12—7	3.0	(+)	1.0	0.45	0.55	0.81		
		13—7	3.0	+						
Hed.	12—7	14—7	3.0	(+)	1.2	0.2	1.0	0.2		Org.

 $\theta$  = Keine Ger. innerhalb der Versuchszeit.

Die Ergebnisse nun, die wie mit verschiedenen Zsp. und Magnesiumplasma bei Zimmertemperatur (20—22 Grad) erzielten, weichen nicht wesentlich von denen ab, die wir bei Eisschrantemperatur sahen, nur dass sie etwas stärker waren, häufiger und bei zeitlicher Beobachtung früher auftraten (Tabelle 7). Auch bei Zimmertemperatur trat nie Ger. auf, wenn wir mit Zsp. mengen von 1.0—1.5  $\text{cm}^3$  arbeiteten, dagegen war eine solche oft ab 2.5  $\text{cm}^3$ , immer bei 3.0  $\text{cm}^3$  zu erzielen. Auch hier scheinen die Fälle von Paralyse und vielleicht auch jene von Lues cerebri stärker zu

reagieren z. B. Fall Ber. der schon bei  $2.0 \text{ cm}^3$  Ger. aktiv war. Ein deutlicher Zusammenhang mit dem Eiweissgehalt der Zsp. ist auch hier nicht festzustellen, worauf nach Vorführung aller Versuche noch eingegangen werden wird.

### III. Versuche mit Oxalatplasma.

Besonders interessant besonders im Hinblick auf die bisher geschilderten Versuche waren nun die, die wir mit *Oxalatplasma* angestellt haben. Wie schon erwähnt, verwendeten wir nicht Ammoniumoxalat, wie Dyckerhoff (l. c.) und seine Mitarbeiter, sondern Natriumoxalat. Wir bedienten uns einer 2 %igen Natriumoxalatlösung und setzten zu  $1 \text{ cm}^3$  dieser Lösung  $9 \text{ cm}^3$  Blnt. Nach gutem Schütteln wurde sofort 45—60 Minuten zentrifugiert. Wie schon erwähnt wichen wir hier von der Technik von Dyckerhoff und seinen Mitarbeitern ab; wir halten es aber für sehr wichtig, den unbestimmten Faktor der Thromboeyten auszuschalten. Vergleichsversuche zwischen einem Plasma, das 10 Min. und einem solchen das 45—60 Min. zentrifugiert war, gaben sehr geringe Unterschiede in der Ger. zeit. (Pr. Nr. 157). Ferner wurde zuerst nach dem Vorgange von Dyckerhoff, sowie Kürten und Harzer, mit Wasser in der Weise verdünnt, dass zu 1 Teil Oxalatplasma 4 Teile destillierten Wassers kamen. Doch erwies sich, wie schon erwähnt, die Wasserverdünnung als nicht wesentlich. Aus Ersparnisgründen gingen wir mit der Plasmamenge bis auf  $0.05 \text{ cm}^3$  herab, wobei sich freilich herausstellte, dass sich mit der Herabsetzung der Plasmamenge die Ger.zeit verlängert (Tab. 8). Nach den mit anderen Plasmen gemachten Erfahrungen liessen wir die Versuche parallel im Eisschrank und bei Zimmertemperatur ablaufen. Der erste Versuch (Pr. Nr. 60), bei dem wir  $3 \text{ cm}^3$  einer Zsp. mit erhöhtem Eiweissgehalt verwendeten, zeigte nach 24 St. ein stärkeres Ergebnis, als es bisher mit den anderen Plasmen erhalten worden war. Die Probe, die bei Zimmertemperatur stehen gelassen worden war, erwies sich als vollkommen fest, und auch jene, die im Eisschrank aufbewahrt worden war, zeigt ein grosses Gerinnsel bei ziemlich zäher Flüssigkeit. Auch die Kontrolle mit  $\text{CaCl}_2$  war fest und zeigte ein grosses Gerinnsel. Eine Zwischenbeobachtung nach 3 Stunden hatte ergeben, dass schon nach dieser Zeit die drei Röhren Ger. erscheinungen gezeigt hatten. Es war daher notwendig, hier eine

Tabelle 8.

**Tabelle 8.**  
Verschiedene Mengen des Oxalatplasma. Zimmertemperatur.

	Liq. Säh.					Liq. Ähm.		Liq. Ähl.				Liq. Gust.			K <sub>1</sub>	K <sub>2</sub>	K <sub>3</sub>	K <sub>1</sub>	K <sub>5</sub>	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	
21°																				
Liquor .....	0.5	1.0	2.0	1.0	2.0	1.0	1.0	1.0	2.0	1.0	2.0	1.0	1.0	1.0	—	—	—	—	—	
0.9 % NaCl .....	0.5	1.0	—	1.0	—	—	—	1.0	—	1.0	—	—	—	—	0.9	1.0	1.9	1.9	2.0	
0.5 % CaCl <sub>2</sub> .....	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0.1	—	0.1	0.1	—	
Oxal. Plas. ....	0.025	0.05	0.05	0.1	0.1	0.025	0.05	0.05	0.05	0.1	0.1	0.025	0.5	0.1	0.025	0.025	0.05	0.05	0.1	
Gerinnung nach .....	0	165'	38'	107'	30'	255,	82'	165'	33'	107'	30'	0 ?	92'	n.T.	57'	0	165'	n.T.	0	
Stärke der Ger. nach 20	0	((+))((+))((+))((+))((+))	((+))((+))((+))((+))((+))	((+))((+))((+))((+))((+))	((+))((+))((+))((+))((+))	((+))((+))((+))((+))((+))	((+))((+))((+))((+))((+))	((+))((+))((+))((+))((+))	((+))((+))((+))((+))((+))	((+))((+))((+))((+))((+))	((+))((+))((+))((+))((+))	((+))((+))((+))((+))((+))	0	(+)	(+)	((+))((+))((+))	0	+	+	+
St. 21° .....																				

St. 21° .....  
Gerinnung nach .....  
Stärke der Ger. nach 20 .....  
Oxal. Plas. ....  
0.5 % CaCl<sub>2</sub> .....

n. T. = Ger. trat erst am nächsten Tag auf.  
 0 = keine Ger. innerhalb der Beobachtungszeit.

Tabelle 9.  
Oxalatplasma.

Name	Liquor- menge	Serum- menge	Ergebnis Eisschr.	Ergebnis Zimmer- temp.	CaCl <sub>2</sub> Kontroll.		Bem.
					Eis- schr.	Zt.	
MA + Ni	3.0		29'	21' (19'?)	230'	26'	
Ri	0.65		0	24 St. Sp.			
Ma.		0.05	24 St. Sp.	24 St. +			
Ca.	1.5		293'	47'	24 St.	47'	
HA.		0.1	24 St. Sp.	24 St. +			

genaue zeitliche Beobachtung des Gerinnungsverlaufes einzuführen. Über den nächsten Versuch (Pr. Nr. 61, Tab. 9) erfahren wir, dass die Ger. von 3 cm<sup>3</sup> Zsp. schon nach 19 Min. begann und zwar in dem Röhrchen, das bei Zimmertemperatur stehen gelassen worden war. Die Recalcifizierungskontrolle begann erst nach 26 Min. zu gerinnen; ferner zeigten 3 cm<sup>3</sup> eines Mischliquors, welche Probe im Eisschrank gestanden war, nach 34 Min. Ger. beginn, während die zugehörige CaCl<sub>2</sub>-Kontrolle erst nach 230 Min. sichere Ger. aufwies. In einem weiteren Falle dieser Tabelle liess sich schon mit 1.5 Zsp. Ger. erzielen und zwar bei Zimmertemperatur zu gleicher Zeit mit der Recalcifizierungskontrolle. Die im Eisschrank aufbewahrte Probe zeigte eine deutliche Ger. erst nach 5 St., die zugehörige CaCl<sub>2</sub>-Kontrolle nach ca. 10 St. Diese Zsp. war jedoch nicht ganz einwandfrei, da sie eine geringe Blutbeimengung hatte, wenn auch der Eiweissgehalt normal war. Die Versuche mit Oxalatplasma erweisen sich also als sehr empfindlich, und es mussten die quantitativen Verhältnisse genau geprüft werden. Vor allem fiel uns auf, dass sich das Oxalatplasma beim Aufenthalt im Eisschrank abschwächt [siehe auch Dyckerhoff und seine Mitarbeiter (l. c.)], was am deutlichsten an den Recalcifizierungskontrollen zu sehen war (Abb. 2). In dieser Abbildung haben wir der besseren Orientierung halber die reciproken Ger. zahlen (v) an der Ordinate verzeichnet, das sind die Zahlen, die sich ergeben, wenn man 100 durch die Gerinnungszeit dividiert  $v = \frac{100}{t_{\text{Ger.}}}$ . Wie wir später sahen sind

in ähnlicher Weise Wöhlisch, Diebold und Kiderlen (52) vorgegangen, die als Mass für die Ger. vorgänge die Grösse  $v = 1/t_F$  annah-

Tabelle 10.  
Verschiedene Liquormengen. Oxalatplasma. Zimmertemperatur.

Verschiedene Liquormengen. Oxalatplasma. Zimmer temperaturen.

Temp.: 1, 2, 3, 4 u. 21 . . 20.5° alle anderen proben 21.5°	Liq. Er.		Liq. Sel.		Liq. E. Joh.				Liq. Lindb.				Liq. Knopp				Liq. Mull.				K <sub>1</sub>	K <sub>2</sub>
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Liquor . . . . .	1.0	1.5	1.0	1.5	0.25	0.5	1.0	1.5	0.25	0.5	1.0	1.5	0.25	0.5	1.0	1.5	0.25	0.5	1.0	1.5	—	—
0.9 % NaCl. . . .	0.5	—	0.5	—	1.25	1.0	0.5	—	1.25	1.0	0.5	—	1.25	1.0	0.5	—	1.25	1.0	0.5	—	0.9	1.4
0.5 % CaCl <sub>2</sub> . .	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0.1	0.1
Oxal. Plasma . .	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Ger. nach . . . .	48'	27'	62'	35'	n.T.	n.T.	42'	29'	n.T.	165'	45'	46'	n.T.	44'	25'	24'	n.T.	165'	60'	95'	73'	19'
Stärke der Ger.																						
nach 20 St. Zl.	+	+	+	+	+	(+)	+	+	+	+	+	+	+	(+)	+	+	+	+	+	+	+	+

von 19—10—13.

Oxal. Plasma 1, 2, 3, 4, 21 vom 20—9—13, alle anderen Proben vom 19—10—13.

men, wo  $t_F$  die Ger. zeit darstellt. Diese Erscheinung spielt jedoch keine ausschlaggebende Rolle, da es sich ja meist um relative Verhältnisse innerhalb eines Versuches handelt. Auf eine Erscheinung sei nur kurz in diesem Zusammenhang hingewiesen, das ist Folgendes: die Abschwächung des Oxalatplasmas zeigt sich deutlich in den Recalcifizierungskontrollen, ist aber meist in den mit Zsp. versetzten Röhren kaum zu beobachten. Wir haben diese Erscheinung das »Kreuzphänomen« genannt. Seine Erklärung ist nicht leicht. Sie wird später zu geben versucht werden.

In den folgenden, Versuchen wurde mit *Oxalatplasma* und *Zimmertemperatur* gearbeitet, und es wurde versucht einen Über-

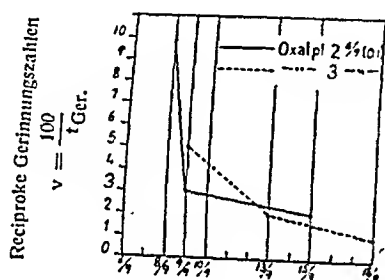


Abb. 2. Altern des Oxalatplasma.

blick über die *quantitativen Verhältnisse* zu bekommen. Tabelle 10 zeigt die Verkürzung der Ger. zeit bei Erhöhung der Menge der Zsp. Wir wir aus der Recalcifizierungskontrolle sehen (Ger. zeit 19 Minuten) war das Plasma relativ frisch. Unter diesen Verhältnissen erhielten wir in allen untersuchten Fällen eine Ger. aktivität der Zsp. bis  $0.25 \text{ cm}^3$  hinunter. Freilich trat bei der letztgenannten Menge der Zsp. die Ger. recht verzögert auf. Von Wichtigkeit ist auch zu wissen, dass nicht alle Plasmen gleichmässig reagieren. Darüber orientiert uns Tabelle 11. Hier werden nebeneinander drei Plasmen zur Reaktion gebracht, von denen zwei an Schizophrenie leidenden Patienten entnommen sind, während eines normal ist. Wir sehen, dass das Normalplasma doch am besten reagierte. Es empfiehlt sich daher, sich wenn möglich zu den Versuchen mit Zsp. eines *Normalplasmas* zu bedienen. Auf Einzelheiten über solche Versuche wird an anderer Stelle hingewiesen werden. Es war weiter von Wichtigkeit festzustellen, ob die Ger. aktivität der Zsp. mit der Zeit schwächer wird. Tabelle 12 belehrt



Tabelle II.  
Verschiedene Plasmen.

21°	Liquor Th.			Liquor Opp.			Liquor L.ö.			K <sub>1</sub>	K <sub>2</sub>	K <sub>3</sub>	Plasma 1: L. C. Schlz. Plasma 2: norm. Plasma 3: A. J. Schlz.
Liquor .....	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	—	—	—	
0.9 % NaCl .....										0.9	0.9	0.9	
0.5 % CaCl <sub>2</sub> .....										0.1	0.1	0.1	
Oxal. Pl. v. 20.9 ..	10.1	20.1	10.1	20.1	20.1	20.1	20.1	20.1	20.1	10.1	20.1	20.1	
Gerinnung nach ....	n.T.	20'	n.F.	n.F.	n.T.	9	9	n.T.	9	18'	26'	37'	
Stärke der Gerinnung													
nach 24 St. 21° gefärbt	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)				

9 = Keine Ger. innerhalb der Versuchszeit.

Tabelle 12.

Liquorkategorien. Versch. Alter. 19 u. 20. 10.

21.5.  Liquor ..... 0.9 % NaCl ..... 0.5 % CaCl <sub>2</sub> ..... Oxal. Pl. v. 19—10 .... Gerinnung nach ..... Stärke der Gerinnung nach 20 St. 21.5° gefärbt	K <sub>2</sub> 20—10		1.4	0.1	0.1	15'	++
	K <sub>1</sub> 19—10		1.4	0.1	0.1	14'	++
	Cyst. liq. Ljung. v. 27—9	1.5			0.1	12'	+/+
	Spin. liq. Erless. v. 28—9	1.5			0.1	22'	++
	Cyst. liq. Isaacs. v. 1—10	1.5			0.1	27'	++
	Cyst. liq. Bran. v. 25—9	1.5			0.1	22'	++
	Spin. liq. B. Jonss. v. 25—9	1.5			0.1	39'	++
	Cyst. liq. Janss. v. 11—10	1.5			0.1	21'	+/+
	Cyst. liq. Brun. v. 30—9	1.5			0.1	17.5'	+
	Spin. liq. Dahl. v. 27—9	1.5			0.1	21'	++
	Cyst. liq. Blomk. v. 4—10	1.5			0.1	30'	++
	Cyst. liq. Hes. v. 4—10	1.5			0.1	30'	++
	Cyst. liq. Nils. v. 4—10	1.5			0.1	30'	++
	Spin. liq. Jac v. 12—10	1.5			0.1	30'	++
	Cyst. liq. Pet. v. 9—10	1.5			0.1	30'	++
	Cyst. liq. Sv. v. 18—10	1.5			0.1	20'	++
	Cyst. liq. Hu. v. 14—10	1.5			0.1	61'	(+)
	Cyst. liq. Da. v. 14—10	1.5			0.1	30'	++
	Cyst. liq. E. v. 14—10	1.5			0.1	30'	+

Tabelle 13.  
Bedeutung von  $p_H$

Liquor 21°	$p_H$	Gerinnung nach			Stärke der Ger. nach 20 St.			Vers. Nr.	Oxal. Pl.	
		0.5	1.0	1.5	0.5	1.0	1.5			
Isac. ....	7.91		62'	38'		+++	+++	91	1 v. 20/9	
Lind. ....	7.52		300'	72'		++	++	,	,	
Brund. ....	8.54		n.T.	468'		(+)	+	,	,	
Nils. ....	8.49		0	720'		0	(+)	92	4 v. 20/9	
Blom. ....	7.92		0	510'		0	++	,	,	
Linds. ....	7.03		0	0		0	0	,	,	
Nordst. ....	8.18	240'	30'	29'	++	+	++	99	FD v. 19/10	
Karls. ....	7.61	240'	29'	29'	+	++	++	,	,	
Sm. ....	8.31	240'	31'	29'	++	+	+++	,	,	Ventrikell.
Irv. ....	7.04		24'					108	Ma v. 15/11	
Hegv. ....	8.05		24'					,	,	
And. ....	6.73		24'					,	,	

n. T. = Ger. am nächsten Tag

0 = Keine Ger. innerhalb der Versuchszeit.

uns darüber. Die der Tabelle zu Grunde liegenden Versuche wurden am 19. und 20. Oktober vorgenommen. Wir sehen, dass es nicht auf das Alter der Zsp. ankommt. Der nur 1 Tag alte Liquor Pet. hat ungefähr dieselbe Ger. zeit wie der 25 Tage alte Bran. Die kürzeste Ger. zeit hat der 20 Tage alte Liquor Brun., die längste der 5 Tage alte Hu. Aus der Tabelle ist weiter zu sehen, dass *Spinal- und Cysternenflüssigkeiten kaum einen Unterschied* in ihrer Ger. aktivität haben. Da Astrup (2) für das Thrombin einen *besonderen  $p_H$*  je nach der Lösung als Optimum annimmt, musste geprüft werden, ob  $p_H$  der Lösung eine Rolle in bezug auf die Ger. aktivität spielt. Tabelle 13 belehrt uns darüber. In Versuch 99 der Tabelle sehen wir trotz verschiedenen  $p_H$  die gleich Ger. zeit von 1.5 cm<sup>3</sup> Zsp. Das Gleiche gilt für Versuch 108. Auch die beiden Versuche 92 und 91 zeigen keinen Parallelismus zwischen  $p_H$  und Ger. zeit. Tabelle 14 zeigt das Ergebnis eines interessanten Versuches. Zufälligerweise erhielten wir an ein und demselben Tage alle 3 Liquorkategorien, nämlich eine Spinal-, einen Cysternen- und einen *Ventrikelliquor*. Während die beiden ersteren dasselbe Resultat in bezug auf Ger. zeit darboten, zeigte demgegenüber der Ventrikelliquor eine deut-

Tabelle 14.

Liquorkategorien,  $p_H$ , Oxalatplasma (0.1) 21°.

Name	vom	Kateg.	$p_H$	Ges. Eiw.	Menge	Gerinnung nach	Bem. u. Diagnos.
Wl.	19—11	Lumbal.	6.07	1.0 T.	1.5	27'	trüb, Kopfsch.
Kvi.	20—11	Cystern.	6.43	1.0 T.	1.5	27'	trüb, Haem. cer.
Krist.	21—11	Ventric.	7.18	0.5 T	1.5	13'	Klar, Hydroc.
					1.4 0.9 % NaCl + 0.1 0.5 % CaCl <sub>2</sub>	67'	Kontr. Recalc.

lich herabgesetzte Ger. zeit. Die Ventrikelflüssigkeit entstammte einem Fall von Hydrocephalus und bot den niedrigen Eiweissgehalt von 0.5 Teilstrich = ea. 10 mg %. Dieser Befund ist für die Theorie des Phänomens von grosser Bedeutung. Auch hier ist kein Parallelismus zwischen  $p_H$  und Ger. zeit zu beobachten.

Fassen wir nun das Wesentliche der Ergebnisse der Magnesiumsulfat- und Oxalatplasma-Versuche nach der Richtung der Klärung der Ger. aktivität der Zsp. zusammen, so wäre zu sagen:

1) Mit Magnesiumsulfatplasma zeigt die Zsp. im Eissehrankversuch nur selten Ger. aktivität, wobei anseheinend Paralyse und eiweissreiche Zsp. bevorzugt werden. Die CaCl<sub>2</sub>-Kontrollen sind stets negativ, doch lässt sich bei höheren Liquormengen eine Aktivierung mit CaCl<sub>2</sub> vollziehen.

2) Mit Magnesiumsulfatplasmen bietet die Zsp. bei Zimmertemperatur häufiger ein positives Ergebnis in bezug auf Ger. aktivität usw. etwa von 2 em<sup>3</sup> an. Die CaCl<sub>2</sub>-Kontrollen sind positiv und zeigen ein Optimum.

3) Bei Verwendung von Oxalatplasmen und bei Zimmertemperatur zeigt sich bei günstigen Versuchsbedingungen so gut wie immer die Ger. aktivität der Zsp., wobei mit steigender Menge der Zsp. die Ger. zeit sinkt, und die Ger. oft früher eintritt als in den CaCl<sub>2</sub>-Kontrollen, die ein deutliches Optimum haben.

4) Die Ger. aktivität der Zsp. ist unabhängig vom  $p_H$  und der Zeit der Aufbewahrung, während das Plasma altert («Kreuzphänomen»).

5) Hat die Zsp. die Ger. aktiviert, so ist sie nach dieser Richtung hin erschöpft, so dass die vom Gerinnsel abgegossene Flüssigkeit die Ger. nicht mehr aktiviert, während es bei den Recalcifizierungskontrollen der Fall ist.

Viele dieser Punkte sprechen schon mit grosser Deutlichkeit dagegen, dass, wie man auf den ersten Blick annehmen könnte, die Ger. aktivität die alleinige Folge des Ca-Gehaltes der Zsp. ist. Über die weiteren Folgerungen aus obigen Ergebnissen wird erst die Rede sein können, wenn über die weiteren Versuche zur Klärung der Na'ur der Ger. aktiven Stoffe in der Zsp. berichtet ist.

#### IV. Besondere Versuche.

Wir haben, wie gleich vorausgeschickt sei, uns von Anfang an der Ansicht zugeneigt, dass in der Zsp. Thrombokinase vorhanden sein könne. Über die chemische Natur der gerinnungsaktiven Zellstoffe [Wöhlisch (49)] gehen die Meinungen der Autoren noch auseinander, doch ist heute wohl die Annahme begründet, dass es sich hierbei um ein Lipoid handelt und zwar nach Howell (27) ein Kephalin. Es lag ja nun die Möglichkeit nahe, dass sich in der Zsp. bei ihren grossen Beziehungen zum Gehirnstoffwechsel eine kephalinartige Substanz vorfinde. Da das Kephalin ein ätherlösliches Phosphatid darstellt, haben wir Zsp. mit der gleichen Menge Äther ein oder mehrmale *geschüttelt*, dann absetzen gelassen, den Liquor mit möglichster Ausschaltung der Zwischenschicht abfließen gelassen und nach Verdunsten des Äthers zum Versuch angesetzt. Wir wollen hier zuerst die Versuche mit *Magnesiumsulfat plasma* besprechen. Die ersten Versuche (P. Nr. 35 und 37) bestätigten schon unsere Vermutung, doch waren sie nicht deutlich genug, weil der native Liquor selbst eine relativ schwache Ger. aktivität aufwies. Das Gleiche gilt für den nächsten Versuch (Pr. Nr. 38). In einem weiteren Versuch (Pr. Nr. 39) war die Erscheinung schon deutlich, da sich bei 2.5 cm<sup>3</sup> der nativen Zsp. ein deutliches Fibrinnetz erzielen liess, während der mit Äther geschüttelte Liquor vollkommen Ger. inaktiv blieb. Sehr deutlich war das Ergebnis eines anderen Versuches (Pr. Nr. 43), das in Tabelle 15 und Abb. 4 niedergelegt ist. Hier zeigten 3 cm<sup>3</sup> des nativen Liquors, mit 0.05 cm<sup>3</sup> Magnesiumsulfatplasma angesetzt, bei Zimmertemperatur eine sehr starke Ger. aktivität während der mit Äther geschüttelte

Tabelle 15.

 MgSO<sub>4</sub> Plasma. Äthervorbehandl. des Liquor.

Zt	Liquor T.A.		Serum Ma.		K <sub>1</sub>	K <sub>2</sub>
	nativ	m. Äther vorbeh.	nativ	m. Äther vorbeh.		
Liquor .....	3.1	3.1	—	—	—	—
Serum .....	—	—	0.1	0.1	—	—
0.9 % NaCl.....	—	—	0.9	0.9	3.0	0.9
0.5 % CaCl <sub>2</sub> .....	—	—	—	—	0.1	0.1
MgSO <sub>4</sub> Plasma Ma. .	0.05	0.05	0.05	0.05	0.05	0.05
Ergebnis nach 24 St.						
Zimmertemp. ....	+++	0	++	++	++	+

0 = Keine Ger. innerhalb der Versuchszeit.

Liquor vollkommen Ger. inaktiv war. Unter den gleichen Bedingungen konnten wir ein ähnliches Resultat mit 2 cm<sup>3</sup> Zsp. erzielen (Pr. Nr. 46), und auch die folgenden Versuche zeigten das gleiche Resultat. Wir können also wohl sagen, dass die in der Zsp. vorhandene Ger. aktive Substanz bei Anwendung von Magnesiumsulfatplasma durch Schüttelung mit Äther aus ihr entfernt wird. Interessanterweise ist das nun bezüglich des Serums nicht der Fall, wie uns unter vielen aus Versuch Pr. Nr. 50 (Tabelle 15) ersichtlich wird. Wir sehen hier, dass das Serum nach Ätherschüttelung die gleiche Ger. aktivität beibehält wie das native Serum. Dies würde auch mit den Angaben der Litteratur übereinstimmen, die durchwegs besagen, dass das im Serum enthaltene Thrombin, wie auch das Prothrombin, in Äther nicht löslich sind. In Tabelle 16 sehen wir weiter einen Versuch, der diesbezüglich von Bedeutung ist, er betrifft die Erhitzung auf 56 Grad. Wie ersichtlich, wird dadurch das Serum vollkommen Ger. inaktiv gegenüber Magnesiumsulfatplasma, die Zsp. aber behält ihre Wirkung vollkommen bei.

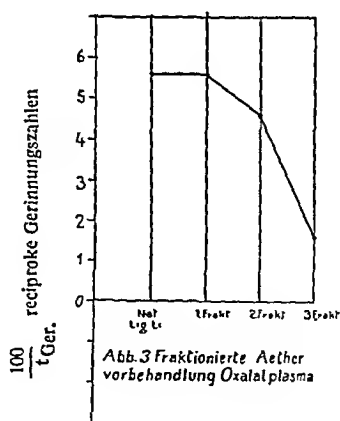
Wir haben also festgestellt, dass bei der Anwendung von Magnesiumsulfatplasma und bei Zimmertemperatur der Zsp. die Ger. aktivität durch Ätherschüttelung genommen wird, während Inaktivierung bei 56 Grad die Wirkung nicht beeinflusste. Die Versuche mit Oxalatplasma ergaben jedoch ein etwas anderes Resultat. Die Tabelle 17 zeigt die Resultate solche Versuche (Pr. Nr. 126 und 127). Die Technik der Ätherschüttelung war die gleiche wie mit Mag-

Tabelle 16.

MgSO<sub>4</sub> Plasma. Inaktivierung des Liquor.

	Liquor Hedv.			Serum Ma.		K
	nativ	nativ	½ St 56°	nativ	½ St. 56°	
Liquor .....	2.9	2.35	3.0	0.1	0	
Serum .....				0.1	0.1	
0.9 % NaCl ..	0.6	1.15	0.5	1.0	1.0	1.0
0.5 % CaCl <sub>2</sub> ....						0.1
MgSO <sub>4</sub> Plasma Ma.	0.05	0.05	0.05	0.05	0.05	0.05
Ergebnis nach ..	Eisschr.	Zt.	Zt.	Zt.	Zt.	Zt.
24 Stunden ....	((+))	(+)	(+)	++	θ	++

nesiumsulfatplasma. Da, wie wir aus anderen Versuchen wissen, sich der Äther leicht erschöpft, wurde bei vielen Versuchen fraktioniert geschüttelt d.h. der nach Schüttelung vom Äther getrennte Liquor wurde wieder mit neuem Äther geschüttelt u.s.w. So entstanden mehrere Fraktionen. Aus Tabelle 17 ist ersichtlich, dass der



mit Äther geschüttelte Liquor Li. 1 erst nach 65' gerann, der native nach 27', ebenso Zsp. Gu. Hier zeigte die erste mit Äther geschüttelte Portion der Zsp. eine Ger. zeit von 193' die zweite Portion eine solche von 308', während der native Liquor schon nach 25' zur Ger. aktivierte. Bei Zsp. Li. 2 ist es interessant, dass hier die relativ kurze Ger. zeit des nativen Liquors (18') durch die

Tabelle 17.

Aethervorbehandlung des Liquor. Oxalatplasma.

	Liq. Li 1			Liq. Gu.			Liq. Li 2				Liq. John.			K <sub>1</sub>	K <sub>2</sub>	K <sub>3</sub>	K <sub>4</sub>
	nat.	vorb.		nat.	vorb.	vorb.	nat.	vorb.	vorb.	vorb.	nat.	vorb.	vorb.	K <sub>1</sub>	K <sub>2</sub>	K <sub>3</sub>	K <sub>4</sub>
		1.	Frakt.		1.	2.		1.	2.	3.		1.	2.				
Temp: 1, 2, 13: 21°	1	2		3	4	5	6	7	8	9	10	11	12	13	14	15	16
3, 4, 5, 14 . . . 19°	1.3	1.3		1.0	1.0	0.95	1.0	1.0	1.0	1.0	1.0	1.0	1.0	—	—	—	—
6, 7, 8, 9, 15 . . 20°	—	—		—	—	0.05	—	—	—	—	—	—	1.2	0.9	0.9	0.9	0.9
10, 11, 12, 16 . . 20°	—	—		—	—	—	—	—	—	—	—	—	—	0.1	0.1	0.1	0.1
Oxal. Pl. . . . .	0.1	0.1		0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Ger. nach . . . . .	27'	65'	25'	193'	308'	18'	22'	66'	55'	610'	11:40'	19'	18'	18'	18'	20'	20'

Oxal. Plasma 1, 2, 13: Ma. 15—12—43

3, 4, 5, 14: Ma. 15—12—43

6, 7, 8, 9, 15: Ma. 26—12—43

10, 11, 12, 16: Ma. 26—12—43



Tabelle 18.

Inaktivierung des Liquor. Oxalatplasma.

Liquor	Menge	Temp.	Zustand	Gerinnung nach	Versuch N:r
Eng. ....	1.0	32°	nativ	0	138
„ ....	1.5	32°	nativ	46'	134
„ ....	1.5	32°	½ St. 56°	0	134
„ ....	1.3	32°	nativ	45'	135
„ ....	1.5	32°	½ St. 56°	0	135
Berl. ....	1.5	33°	nativ	12'	140
„ ....	1.5	33°	½ St. 56°	17'	140
Karls. ....	1.5	33°	nativ	28'	140
„ ....	1.5	33°	½ St. 56°	36'	140
Ros. ....	1.5	31°	nativ	35'	141
„ ....	1.5	31°	½ St. 56°	52'	141
Eriks. ....	1.5	31°	nativ	21'	141
„ ....	1.5	31°	½ St. 56°	21'	141
Westb. ....	1.5	31°	nativ	21'	141
„ ....	1.5	31°	½ St. 56°	21'	141
Me. ....	1.5	31°	nativ	21'	141
„ ....	1.5	31°	½ St. 56°	25'	141
Törnquist ..	1.5	31°	nativ	13'	141
„ ..	1.5	31°	½ St. 56°	13'	141
2 Sera ....	0.3	32°	nativ	40'	142
„ (norm.)..	0.3	32°	½ St. 56°	schw. Flock.	142

0 = Keine Gerinnung innerhalb der Versuchszeit.

erste Schüttelung gar nicht beeinflusst wurde, während die zweite Fraktion die Ger. zeit von 22' hatte, die dritte 66'. Dagegen weist bei Zsp. John die erste vorbehandelte Fraktion die Ger. zeit von 610', die zweite eine solche von sogar 1140' auf, während die native Zsp. die Ger. zeit 55' hat. Das Verhalten der Zsp. Li. 2 ist auch aus Abb. 3 ersichtlich. Wir schliessen aus den erwähnten Versuchen, dass beim Magnesiumsulfatplasma eine Ätherschüttelung genügt, um die Ger. aktivität verschwinden zu lassen, während beim Oxalatplasma meist erst die fraktionierte Vorbehandlung mit Äther zur progressiven Aktivitätsherabsetzung führt, die sich beim Serum nur im Oxalatplasma und in sehr geringem Grade äussert. Auch die Inaktivierungsversuche verlaufen mit Oxalatplasma etwas anders als mit Magnesiumsulfatplasma (Tab. 18). Von den hier angeführten Zsp. hat nur eine,

Tabelle 19.

Adsorption d. Liquor nach Bordet und Eluierung des Ads. mit Aether.

21°	Liq. Ekl. nat.	Liq. Ekl. vorbeh.	K
Liquor .....	3.0	3.0	—
0.9 % NaCl .....	—	—	2.9
0.5 % CaCl <sub>2</sub> .....	—	—	0.1
Oxal. Pl. Ma .....	0.2	0.2	0.2
Ger. nach .....	30'	n. T.	?
Adsorptionsmittel mit 'Aether eluiert, Aether verdunstet, Rückstand in 0.9 % NaCl, davon .....	1.0	—	—
0.9 % NaCl .....	—	1.0	1.1
0.5 % CaCl <sub>2</sub> .....	0.1	0.1	
Oxal. Pl. Gy. ....	0.2	0.2	0.2
Ger. nach .....	85'	n.T.	θ

n. T = Ger. am nächsten Tag

θ Keine Ger. innerhalb der Versuchszeit.

die im nativen Zustand relativ gering Ger. aktiv war, nach Inaktivierung bei 56 Grad eine völlige Aufhebung der Ger. aktivität gezeigt, drei blieben durch diesen Eingriff unverändert, zwei wurden nur sehr mässig, eine etwas mehr abgeschwächt. 0.2 cm<sup>3</sup> eines Normalserums wurden nach Erwärmung auf 56 Grad vollkommen Ger. inaktiv gemacht, während zwei andere Sera, deren Ger. zeit im nativen Zustand 40' war, nach Inaktivierung bei 56 Grad erst am nächsten Tag eine fraglich Ger. zeigten, die aber wie eine Flockung aussah.

Bevor wir zur Diskussion dieser Ergebnisse übergehen, sei weitere aufklärender Versuche gedacht. Es handelt sich um die *Prothrombinadsorption*. Diese erfolgte nach Bordet (4, 5) durch dreimaliges Schütteln mit tertiärem Calciumphosphat und nach jedem Schütteln folgendem Zentrifugieren. Hiezu sei bemerkt, dass die neueren Autoren (Dyckhoffer und Mitarbeiter u. a.) in dieser Weise vorgehen, während Bordet sich besonders bereiteter kolloidaler Tricalciumphosphatlösung bedient. Die Adsorption soll nach ihm und den meisten Ger. forschern spezifisch für Prothrombin sei. Wir berichten hier über zwei solche Versuche (Pr. Nr. 68 u. 69), die in Tab. 19 dargestellt sind. Hier wurde nach Vorbehandlung

der Zsp. bei Zimmertemperatur mit Oxalatplasma untersucht. Der native Liquor zeigte eine Ger. zeit von 30', der vorbehandelte von vielen Stunden. Wurden die tertiären Calciumrückstände, die der Adsorption gedient hatten, mit Äther eluiert, der Äther verdunsten gelassen, und der Rückstand in 0.9 %iger NaCl-Lösung aufgenommen, so zeigte die Flüssigkeit, mit Oxalatplasma und  $\text{CaCl}_2$  zusammengebracht, vollständige Ger. nach 85', während die Recalcifizierungskontrolle allein erst nach 16 Stunden gerann. Wir werden auf diesen Versuch später noch zurückkommen. In einem anderen Versuche (Pr. Nr. 132) zeigte die Zsp. nach Vorbehandlung keine Ger. aktivität, während 1.5 cm<sup>3</sup> der nativen Flüssigkeit das Oxalatplasma nach 11' zur Ger. brachte. Hier wurden die Calciumphosphatrückstände zuerst mit Äther, dann mit 0.9 %iger NaCl-Lösung eluiert. Der Ätherrückstand wurde nach Verdunsten in 0.9 %iger NaCl-Lösung aufgenommen; das NaCl-Eluat wurde zentrifugiert und nach Abgiessen in den Versuch eingestellt. Während die Zsp. ohne Zusatz nach 46' Ger. aktiv wirkte, war es nach Zusatz der Eluate innerhalb 43' der Fall.

Von grossem Interesse sind auch die Versuche, bei denen die Prothrombinadsorption am Oxalatplasma erfolgte. Hier erhielten wir ganz klare Resultate (Pr. Nr. 101, Tab. 20). Aus dieser Tabelle ersehen wir, dass 3 Zsp., die mit nativem Oxalatplasma die Ger. zeiten 17' 17', 14' hatten, mit vorbehandeltem Oxalatplasma nicht gerannen. Ein Normalserum zeigte dagegen mit nativem und vorbehandeltem Oxalatplasma die gleichen Werte. In einem anderen Versuch (Pr. Nr. 138) zeigte ein Normalserum mit vorbehandeltem Oxalatplasma bei 32 Grad die Ger. zeit 162', mit nativem 192'. Eine Zsp. (Pr. Nr. 139) wies bei 32 Grad in der Menge von 1.5 cm<sup>3</sup> mit nativem Oxalatplasma die Ger. zeit 12' auf, mit vorbehandeltem trat keine Ger. auf. Diese Versuche würden für ein isoliertes Vorkommen von Thrombokinase in der Zsp. sprechen; würde sich Thrombin oder Prothrombin in der Zsp. finden, so müsste auch nach der Prothrombinadsorption des Plasmas Ger. auftreten, wie es ja die Sera zeigen. In diesem Sinne sprechen auch die Recalcifizierungskontrollen, die trotz Thrombokinasezusatzes mit dem adsorbierten Plasma negativ blieben (Pr. Nr. 137).

Noch einer Versuchsanordnung sei gedacht, die sich an eine frühere mit Magnesiumsulfatplasma anschliesst. Wie hatten damals gefunden, dass bei Eisschranktemperatur sich eine Ger.

Tabelle 20.

Vorbehandlung des Oxalatplasmats mit tert. Calciumphosphat.

37°	Liquor Li.	Liquor Ols.	Liquor Baekl.	Serum 2 (norm.)	K <sub>1</sub>	K <sub>2</sub>
Liq. oder Ser. ....	1.0	1.0	1.0	0.2	—	—
0.9 % NaCl .....				0.8	0.9	0.9
0.5 % CaCl <sub>2</sub> .....					0.1	0.1
Oxal. Pl. v. 19/10 .....	0.05	0.05	0.05	0.05	0.05	0.05
	nat.	vorb.	vorb.	nat.	nat.	vorb.
Gerinnung nach ....	17'	17'	0	n.T.	n.T.	0
Stärke der Gerinnung nach 20 St. 37° gef. ..	+	f. ++	0	+	+	0
			14'	n.T.	45'	(+)
			+	+	+	

0 = Keine Gerinnung innerhalb der Versuchszeit. n. T. Ger. am nächsten Tage.

Tabelle 21.

Thrombokinaseaktiv. Oxalatplasma.

32°	Liquor Ed. Ol.		Liquor Str.		Liquor Krist.		K <sub>1</sub>	K <sub>2</sub>
Liquor .....	1.0	1.0	1.0	1.0	1.0	1.0	—	—
0.9 % NaCl ....	0.05		0.05		0.05		0.95	0.9
0.5 % CaCl <sub>2</sub> ....							0.1	0.1
Thrombokinase		0.05		0.05		0.05		0.05
Oxal. Pl. Ma vom								
Tage vorher ..	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Gerinnung nach	29'	4'	16'	4'	16'	4'	10'	4'

aktivierung von 1.0 cm<sup>3</sup> Zsp. oder 0.2 cm<sup>3</sup> Serum durch 0.1 cm<sup>3</sup> Thrombokinase nicht durchführen lässt (Tab. 3). Bedient man sich aber des Oxalatplasmas und höherer Temperaturen, so aktivieren Zusätze von 0.05 cm<sup>3</sup> Thrombokinase 1.0 cm<sup>3</sup> Zsp. stark usw. (Pr. Nr. 124, Tab. 21) von 29, 16', 16' auf überall 4', die gleiche Ger. beschleunigung, wie sie auch in den CaCl<sub>2</sub>-Kontrollen nach Thrombokinase zusatz erfolgte. Auch einmal mit Äther geschüttelte Zsp. liess sich so aktivieren. Wurde aber zu einem älteren Serum, das die Ger. zeit 274' hatte, Thrombokinase in derselben Menge zugesetzt, so liess sich eine Beschleunigung von nur 204' erzielen (Pr. Nr. 122). Da das Serum ja vorwiegend Thrombin enthält, lässt sich diese geringe Einwirkung vielleicht verstehen. Ein Versuch (Pr. Nr. 123) sei besonders besprochen. Zu 4 Zsp., die die Ger. zeiten 27', 27', 15', 15' hatten, wurde durch 0.05 cm<sup>3</sup> Thrombokinase die Ger. zeit auf überall 3' beschleunigt. In dieser Versuchsreihe fand sich die Zsp. einer malariabehandelten Paralyse, die, mit Äther vorbehandelt, früher Ger. aktiv wurde (15') als der native Liquor. Leider liess sich bei dem Mangel an Paralysenmaterial ein solches anscheinend paradoxes Ergebnis bisher nicht reproduzieren.

Sehr wesentlich erschien uns auch ein Versuch, den Dyckerhoff und Deschler (11) in ähnlicher Weise ausgeführt haben. Diese Autoren konnten nämlich zeigen, dass durch Ätherextraktion dem Oxalatplasma ein Ger. aktives Lipoid entzogen wird, wobei aber durch nachträglichen Thrombokinasezusatz die Ger.fähigkeit wiederhergestellt werden kann. Wir gingen nun in der Weise vor, dass wir, wie oben geschildert, Magnesiumsulfatplasma mit Äther

Tabelle 22.  
Vorbehandlung des  $MgSO_4$  Plasmas m/Aether.

Zt	Liquor Ni.	Liquor Ni.	K <sub>1</sub>	K <sub>2</sub>	K <sub>3</sub>	K <sub>4</sub>
Liquor .....	3.0	3.0	—	—	—	—
0.9 % NaCl .....	—	—	1.0	1.0	1.1	1.1
0.5 % $CaCl_2$ .....	—	—	0.1	0.1	—	—
$MgSO_4$ Plasma Hi .....	0.05	0.05	0.0	0.05	0.05	0.05
	nativ	vorbeh.	nativ	vorbeh.	nativ	vorbeh.
Ergebnis nach 24 St. Zimmertemp. ....	(+)	(+)	++	θ	θ	θ

θ = Keine Ger. innerhalb der Versuchszeit.

schüttelten und das so vorbehandelte Plasma neben dem nativen mit Zsp. zusammentreten liessen. Auch die Recalcifizierungskontrollen wurden mit beiden Plasmen angesetzt. Tab. 22 (Pr. Nr. 29) zeigt die Ergebnisse eines solchen Versuches. Während 3 cm<sup>3</sup> Zsp. mit nativem und vorbehandeltem Plasma Ger. aktiv geblieben sind, ist die mit nativem Plasma stark positive Recalcifizierungskontrolle mit vorbehandeltem Plasma vollkommen Ger. inaktiv geworden. Daraus ergibt sich, dass für den Ausfall der Probe mit Zsp. die im Plasma enthaltene Thrombokinas keine Rolle spielt, diese also in der Zsp. selbst enthalten sein muss. Ähnliche Versuche mit Oxalatplasma scheiterten bisher an technischen Schwierigkeiten.

Zusammenfassend lässt sich über die Versuche zur Klärung der Ger.phänomene in der Zsp. Folgendes sagen:

1) Ätherschüttelung der Zsp. ruft bei Verwendung von Magnesiumsulfatplasma Ger. inaktivität hervor, während ebenso behandeltes Serum Ger. aktiv bleibt;

2) Halbstündige Erwärmung der Zsp. auf 56 Grad wirkt bei Verwendung von Magnesiumsulfatplasma nicht auf die Ger.aktivität ein, während Serum inaktiv wird.

3) Bei Verwendung von Oxalatplasma wird durch fraktionierte Ätherschüttelung die Ger. aktivität progressiv herabgesetzt, ohne aber vollständig zu schwinden. Mit Serum ist diese Erscheinung nur sehr gering nachweisbar.

4) Erwärmung der Zsp. auf 56 Grad ruft bei Verwendung von Oxalatplasma entweder keine oder nur geringe Herabsetzung

der Ger. aktivität hervor; Zsp., die nur ganz schwache Ger. aktivität zeigen können negativ werden. Sera werden bei dieser Versuchsanordnung meist Ger. inaktiv.

5) Die Vorbehandlung der Zsp. mit tertiärem Calciumphosphat nach Bordet und Verwendung von Oxalatplasma rief stärkere bis schwächere Herabsetzung der Ger. fähigkeit hervor.

6) Die Vorbehandlung des Oxalatplasmas nach Bordet machte die Zsp. Ger. inaktiv, während Sera unbeeinflusst blieben.

7) Äthervorbehandlung des Magnesiumsulfatplasmas schädigt die Ger. aktivität der Zsp. nicht, während die Recalcifizierungskontrollen negativ werden.

8) Thrombokinasezusatz zur Zsp. aktiviert bei Verwendung von Oxalatplasma die Ger. stark, während Sera nur sehr gering beeinflusst werden.

#### *V. Diskussion der Ergebnisse.*

Wir haben in vorausgehenden Zeilen nachzuweisen gesucht, dass die normale Zsp. und auch jene, die von organisch Nervenkranken stammt, die keine groben Permeabilitätsstörungen der Meningealgefäße bieten, Ger. aktiv ist. Diese Eigenschaft ist bei Verwendung von Oxalatplasma noch bei  $0.25 \text{ cm}^3$  nachzuweisen; sie ist bei  $1.5 \text{ cm}^3$  sehr deutlich. Während aber wohl alle Zsp. mit Oxalatplasma bei Zimmertemperatur reagieren, ist bei Verwendung von Magnesiumsulfatplasma und bei Eisschranktemperatur diese Erscheinung selten und anscheinend hauptsächlich bei Paralyse, vielleicht auch Lues cerebri-fällen oder eventuell bei organischen Nervenkrankheiten mit erhöhtem Eiweißgehalt in der Zsp. Bei Zimmertemperatur ist sie hier häufiger und stärker. Dabei verlaufen die Recalcifizierungsversuche mit Magnesiumsulfat im Eisschrank stets negativ. Bei den Versuchen mit Magnesiumsulfatplasma ist bei den Ger. inaktiven Fällen oft eine Aktivierung durch  $\text{CaCl}_2$ -Lösung zu erzielen, nicht durch Thrombokinase. Die Ger. aktivität mit Oxalatplasma ist allen Liquorkategorien eigen, Cysternen- und Lumballiquor scheinen ungefähr gleich zu reagieren, Ventrikelflüssigkeit stärker. Die Eigenschaft der Ger. aktivität der Zsp. bleibt sich beim Lagern im Eisschrank ungefähr gleich, während die Ger. zeit des recalcifizierten Oxalatplasmas beim Altern immer länger wird (»Kreuzphänomen«). Die Ger.

zeit nimmt bei steigenden Liquormengen progressiv ab. Verschiedene Oxalatplasmen reagieren verschieden; Normalplasma scheint Schizophrenenblutplasma überlegen zu sein. Äthervorbehandlung der Zsp. macht diese bei Verwendung von Magnesiumsulfatplasmen Ger. inaktiv, während Sera aktiv bleiben; bei Oxalatplasmen ruft die gleich Vorbehandlung der Zsp. eine fraktionsweise steigende Abschwächung der Ger. aktivität hervor., die bei Seren sehr gering ist. Erhitzung der Zsp. auf 56 Grad lässt stark Ger. aktive Zsp. unverändert, schwächer aktive werden etwas weniger wirksam, ganz gering aktive werden wohl auch negativ. Sera werden durch den gleichen Vorgang meist negativ. Wird die Zsp. nach Bordet adsorbiert, so vermindert sich die Ger. aktivität. Wird Oxalatplasma in der gleichen Weise behandelt, so wird die Zsp. Ger. inaktiv, während Sera aktiv bleiben. Wird Magnesiumsulfatplasma mit Äther behandelt, so bleibt die Zsp. in ihrer Ger. aktivität unverändert, während die Recalcifizierungskontrollen negativ werden. — Ein Antithrombin lässt sich in der Zsp. nicht feststellen; jedoch kann im Serum vorhandenes Anti- oder Metathrombin auf eine zugesetzte Zsp. Ger. verzögernd wirken. Frische Sera und Zsp. scheinen sich in ihrer Ger. aktivität günstig zu beeinflussen (Pr. Nr. 153 und 154).

Wir haben die Ergebnisse noch einmal vorgeführt, um nun in die *Diskussion* einzugehen. Hier wäre vor allem die Frage zu beantworten, ob nicht der *Kalkgehalt* der Zsp. die Ursache ihrer Ger. aktivität ist. Nach Abramson (1) ist der Ca-Gehalt der Zsp. im Mittel  $5.24 \pm 0.08$  mg %. Die oberen und unteren Grenzwerte sind 4.25 und 6.23 mg %. Nach Behrendt (3) soll der Anteil des ionisierten Ca 20 % betragen, also ungefähr 1 mg %. Es würde dann Gesamtkalk und ionisiertes Ca ungefähr die Hälfte der betreffende Werte für das Blut betragen. Nach Sary, Kral und Winternitz (44) entspricht der Ca-Gehalt der Zsp. dem dialysablen des Serums. Broek (6) nimmt auf Grund seiner Untersuchungen an, dass für das ionisierte Ca ein Mittelwert von 1.9 mg % zu beobachten ist. Marraech und Thacker (36) glauben, dass das gesamte Ca in der Zsp. dissoziiert ist. Bei verschiedenen Erkrankungen des Zentralnervensystems und seiner Häute kommen nur geringfügige Erhöhungen der Mittelzahl vor, so dass der Ca-Gehalt der Zsp. ziemlich konstant ist. Es ist daher von vornherein nicht anzunehmen, dass Schwankungen im Ca-Gehalt der Zsp. die Ursache für verschie-



dene Ger. zeiten sind. Dafür aber, dass der Calciumgehalt der Zsp. nicht für das Zustandekommen der Ger. erscheinungen allein anzusprechen ist, sprechen viele Beobachtungen:

1) Bei den Magnesiumsulfatplasma-Eisschrankversuchen tritt nie in den Reeealeifizierungsröhrchen Ger. auf, die aber in einer Reihe von Fällen durch Zsp. zu erzielen ist; also unter diesen Bedingungen ist eine Ger. aktivierung durch bestimmte Stoffe der Zsp. erzeugt.

2) Bei den Magnesiumsulfatplasma-Zimmertemperatur-Versuchen kann man zwar das Plasma reeealeifizieren, aber bei höheren  $\text{CaCl}_2$ -Mengen findet wieder eine Hemmung der Ger. statt (Wöhlisch (49), Kürten (32) u.v.a.) während bei der Zsp. ein Ansteigen der Ger. aktivität mit zunehmenden Mengen der Zsp. im allgemeinen zu beobachten ist.

3) Bei Verwendung von Oxalatplasma und Zimmer- oder Brutschranktemperatur tritt sehr oft die Ger. im Zsp. Röhrchen früher als im reeealeifizierten ein. Besonders auffallend wird diese Erscheinung, wenn das Plasma etwas älter ist.

4) Lässt man in einem Zsp.- und einem Reeealeifizierungsröhrchen Ger. eintreten, entfernt die Gerinnsel aus beiden Röhrchen und setzt neues Plasma zu, dann kommt es im Zsp. Röhrchen nicht mehr zur Ger., dagegen in der Kontrolle.

5) Die gerinnungsaktive Substanz der Zsp. lässt sich durch Ätherschüttelung weitgehend aus der Zsp. eliminieren, während der Ca-Gehalt normal bleibt.

Natürlich ist mit diesen Argumenten, die sich nach unseren Versuchen noch wesentlich vermehren liessen, nur gesagt, dass die wesentliche die Ger. vermittelnde Substanz in der Zsp. nicht das Ca ist; andererseits ist der Ca Gehalt der Zsp. zur Ger. notwendig, was auch daraus hervorgeht, dass Zusatz von Natrium oxaleum zur Zsp. die Ger. verhindert (auch wenn noch nachträglich  $\text{CaCl}_2$  zugesetzt wird. Pr. Nr. 95). Was aber ist nun das Ger. aktive Princip der Zsp.? Ist es das fertige Fibrinferment, das Thrombin (wie wir früher angenommen haben) oder seine Vorstufen, das Prothrombin oder die Thrombokinasen? Oder vielleicht ein bisher unbekannter Faktor? Wir möchten dabei, um nicht den Boden unter den Füßen zu verlieren, uns bei dieser Darstellung an die Fermenttheorie des Ger. vorganges halten und uns der am meisten gebräuchlichen Bezeichnungen bedienen.

Da das fertige Fibrinferment sich im strömenden Blut im allgemeinen nicht findet, ist es auch unwahrscheinlich, dass es in der Zsp. zu finden wäre. Es ist ausserdem thermolabil, also bei 56 Grad inaktivierbar, durch Äther nicht zur Lösung zu bringen u.s.w. Ein Faktor spricht besonders gegen die Anwesenheit des Thrombins in der Zsp. Wird nach Bordet das Prothrombin aus dem Oxalatplasma adsorbiert, dann wird ein so vorbehandeltes Oxalatplasma durch Zsp. nicht zur Ger. gebracht, dagegen durch Serum. Auch schwächt sich das im Serum befindliche Thrombin allmählich ab, indem es in Metathrombin übergeht, was in der Zsp. nicht zu beobachten ist. *Wir können also wohl das Thrombin als Ursache der Ger. aktivität der Zsp. ausscheiden.*

Es wird nun weiter zu diskutieren sein, ob die Thrombokinase oder das Prothrombin oder gar beide zusammen in der Zsp. enthalten sind. Für das Vorkommen von Thrombokinase in der Zsp. sprechen vor allem die Versuche mit Magnesiumsulfatplasma, das ja nach Dyckerhoff und Goossens (14) ein besonders feines Reagens auf Thrombokinase ist. Wir haben gehört, dass Äthererschüttelung der Zsp. diese Ger. inaktiv macht. Andererseits schädigt die Erwärmung der Zsp. auf 56 Grad die Ger. fähigkeit nicht. Mit dem Serum ist es gerade umgekehrt. Nun wissen wir durch viele Autoren [A. Schmidt (42), Morawitz (38), Howell (27), Wöhlisch (49), Dyckerhoff l.c.) u. a.] dass die Thrombokinase in Äther löslich und thermostabil ist. Auch der erwähnte Versuch, dass die Zsp. Ger. inaktiv wird, wenn man sie mit nach Bordet adsorbiertem Plasma zusammenbringt, würde sehr dafür sprechen; denn ist in der Zsp. nur Thrombokinase, im Plasma kein Prothrombin mehr, so kann die Ger. nicht eintreten, während es in Serum wegen des Thrombin (und Prothrombin ?) gehaltenes möglich ist. Ferner: schüttelt man Magnesiumsulfatplasma mit Äther, beraubt das Plasma also seiner Thrombokinase, dann ist das so vorbehandelte Magnesiumsulfatplasma nicht mehr recalcifizierbar, während die Zsp. auf Grund ihres Thrombokinasegehaltes Ger. hervorruft. Dyckerhoff und Deschler (11) berichten ja auch in ihren Ätherversuchen darüber, dass sich aus dem Oxalatplasma durch Vorbehandlung mit Äther ein Ger. aktives Lipoid entziehen lässt, dessen Funktion durch Thrombokinase wiederherstellbar ist. Uns sind freilich solche Versuche mit Oxalatplasma nicht gelungen.

Die eben erwähnten, Versuche würden also einwandfrei für

das *isolierte Vorkommen von Thrombokinese* in der Zsp. sprechen. Doch sind andere Versuche mit Oxalatplasma nicht so eindeutig. Fraktionierte Ätherbehandlung ruft bei Verwendung von Oxalatplasma zwar eine Abschwächung, aber kein Aufhören der Ger. aktivität hervor. Freilich liesse sich dieses Resultat damit erklären, dass bei dieser so empfindlichen Methode trotz des Entzuges der Thrombokinese auf Grund des Ca-Gehaltes der Zsp. es zu einer schwachen Recalcifizierung des Plasmas kommt, dieser also das im Plasma enthaltene Prothrombin und die Thrombokinese aktiviert. Schwieriger zu verstehen sind die Inaktivierungsversuche. Trotzdem wir wissen, dass Thrombokinese durch Erwärmen auf 56 Grad nicht geschädigt wird, können wir besonders bei Ger. schwachen Zsp. eine Verminderung der Ger. aktivität gegenüber Oxalatplasma bemerken, die eigentlich darauf hindeuten würde, dass auch Prothrombin in geringen Menge in der Zsp. enthalten ist. Am stärksten wiegt aber nach dieser Richtung hin jene Versuchsreihe, bei der die Prothrombinadsorption der Zsp. unternommen wurde. Hier konnten wir eine Verlängerung der Ger. zeit bei den adsorbierten gegenüber den nicht vorbehandelten Zsp. nachweisen. Da man im allgemeinen der Ansicht ist, dass die Vorbehandlung mit tertiärem Calciumphosphat für Prothrombin spezifisch ist, so müsste in diesen Fällen Prothrombin in der Zsp. vorhanden sein. Dagegen aber spricht die Beobachtung, dass die an die Niederschläge des tertiären Calciumphosphats gebundenen Stoffe in einem Versuch (Pr. Nr. 134) in Äther eluierbar waren und dann im Versuch eine Beschleunigung der Ger. des Oxalatplasmas hervorriefen. Das Prothrombin aber ist in Äther nicht löslich. Daraus würde vielleicht hervorgehen, dass in einer eiweissarmen Flüssigkeit, wie der Zsp., auch die Thrombokinese mit tertiärem Calciumphosphat adsorbierbar ist.

An sich aber würde das *Nebeneinandervorkommen von Thrombokinese und Prothrombin* in einer fibrinogenfreien Flüssigkeit, wie sie die normale Zsp. darstellt, absolut möglich sein. Schon Morawitz (38) hat festgestellt, dass in Gewebsextrakten sich Prothrombin neben Thrombokinese finden kann. Das wurde besonders von Kraus und Fuchs (31) bestätigt, die beobachtet haben, dass Gewebssäfte in frischem Zustande sowohl Prothrombin als auch Cytozym enthalten, letzteres in besonders reichlicher Menge. Auch in den Blutplättchen ist nicht, wie man früher angenommen

hat, nur Thrombokinasen enthalten, sondern auch Prothrombin [Morawitz (38), Fuchs, Falkenhausen und Hartmann (23)]. Man hält nun das Prothrombin für einen eiweissartigen Körper oder man nimmt an, dass es an Eiweiss gekoppelt ist. Aus den Fuchsschen Versuchen scheint hervorzugehen, dass das Prothrombin wie das Mittelstück des Komplements an durch Salzsäure oder  $\text{CO}_2$  fällbares Globulin gebunden ist usw. im Blute. Es ist nach Dale und Walpole (8) in der Euglobinfraktion enthalten. Das durch  $\text{CO}_2$ -Fällung gewonnene Mittelstück funktioniert gegenüber dem prothrombinfreien Plasma als Prothrombinlösung, die Prothrombinfunktion ist also an die Labilglobuline gebunden. Es ist nun sehr interessant, dass in der normalen Zsp. sich keine mit Salzsäure oder  $\text{CO}_2$  fällbaren Globuline finden, überhaupt keine Euglobuline [Kafka, Ujsaghy u.a.]. Würde also Prothrombin in der Zsp. vorhanden sein, so könnte es nicht an Labilglobuline gekoppelt sein. Fuchs (21) hat ja bekanntlich eine Identität des Komplementmittelstückes mit dem Prothrombin auf Grund solcher und ähnlicher Versuche nachzuweisen geglaubt, was jedoch durch Quiek (40), Wising (48), Wöhlisch (49) u.a. bestritten wird. Es ist nun in diesem Zusammenhange zu berichten, dass Kafka (29) und Goeckel (25) zu gleicher Zeit mit Banchieri (1922)<sup>1</sup> nachgewiesen haben, dass auch die normale Zsp. das Mittelstück der Komplements enthält, ohne über Labilglobuline zu verfügen. Der von Kafka (29) und Goeckel (25) gefundene Körper ist durch Äther ausschüttelbar und wird durch Erhitzung auf 56 Grad inaktiv. Er erinnert daher etwas an die Ger. aktiven Stoffe in der Zsp., doch haben wir ja gehört, dass die Erwärmung auf 56 Grad nur einzelne Zsp. in ihrer Ger. aktivität schädigt und dies nicht weitgehend, und dass auch durch Ätherschüttelung die Ger. aktivität nicht vollständig ausgeschaltet wird, während beide Eingriffe die Mittelstückfunktion unwirksam machen. Immerhin wäre es interessant, die Versuche von Fuchs und seinen Mitarbeitern mit Zsp. wieder aufzunehmen. Wir haben schon mit den Vorbereitungen begonnen.

Wenn wir es also als erwiesen ansehen, dass in der normalen Zsp. Thrombokinasen und etwas Prothrombin enthalten sind, so wäre nun zu diskutieren, wie vom Standpunkt dieser Annahme

<sup>1</sup> Banchieri, Patologia, N:o 328 (1922).

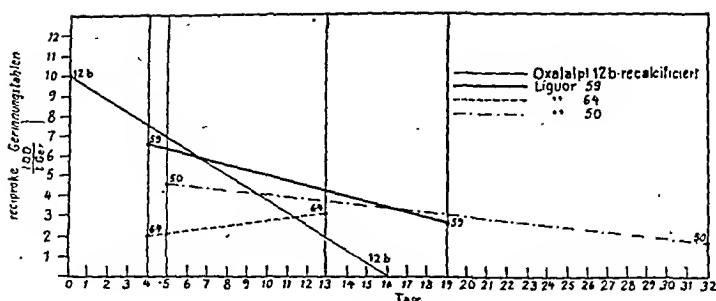


Abb. 4. »Kreuzphänomen«

aus sich die Beobachtung erklärt, dass beim Magnesiumsulfat-plasma-Eisschrankversuch die Recalcifizierungsproben stets negativ ausfielen, während sich die Zsp. durch  $\text{CaCl}_2$  aktivieren lasse, ferner jene, dass im Oxalatplasmaversuch eine äusserst starke Aktivierung der Zsp. durch Thrombokinase erfolgt, während im Serum eine solche »nur schwach nachzuweisen ist, schliesslich der sogenannte »Kreuzversuch«, der darin besteht, dass das Oxalatplasma relativ schnell altert d.h. unwirksam wird, während man in den mit Zsp. beschickten Röhrchen nur in geringen Grade eine Alterung bemerkt, auch dann kaum, wenn man schon unrecalcifizierbares Oxalatplasma nimmt (Abb. 4). Die Erklärung für die Unmöglichkeit, Magnesiumsulfatplasma im Eisschrank zu recalcifizieren, liegt nach den meisten Autoren darin, dass durch die starken Salzkonzentrationen des Plasmas das Prothrombin grösstenteils unwirksam gemacht wird; hinzu kommt die Verlangsamung etwaiger Ger. vorgänge durch den Eisschrankaufenthalt, so dass innerhalb von 24 Stunden jedenfalls Ger. nicht zu beobachten ist. Die Ger. tritt auch nicht auf trotz optimaler Recalcifizierung. Wie wie aber aus Tabelle 6 sehen, lassen sich höhere Mengen von Zsp. durch 0.1 cm<sup>3</sup> 0.5 %iger  $\text{CaCl}_2$ -Lösung zur Ger. aktivieren u.zw. die Zsp. von zwei Paralysen bei 1.0 und 2.0 cm<sup>3</sup>, jene von zwei Nichtparalysen bei 3.0 cm<sup>3</sup>. Eine Erklärung ist schwierig; man muss wohl annehmen, dass in der Zsp. Prothrombin enthalten ist, das aber bei den ungünstigen Versuchsbedingungen im Eisschrank erst bei höheren Mengen von  $\text{CaCl}_2$ -Lösung aktiv wird. Es scheint auch so zu sein dass die Zsp. von Paralytikern mehr Prothrombin enthält als die normale. Auch die Thrombokinaseaktivierung der Zsp. im Oxalatplasmaversuch deutet auf den Prothrom-

bingehalt der Zsp. hin. Im Serum ist wohl relativ wenig reaktionsfähiges Prothrombin enthalten, weshalb die Ger.beschleunigung nur schwach ist. Das Thrombin wird ja durch den Zusatz nicht beeinflusst. Schliesslich der »Kreuzversuch«. Wie ist das »Altern« des Oxalatplasmas zu erklären? Abb. 4 gibt uns ein deutliches Bild des Phänomens. Die Autoren, die diese Erscheinung auch beobachtet haben [Dyckerhoff, Steiner und Miehler (12)] geben keine Erklärung dafür. Der Calciumgehalt der Zsp. kann keine Ursache dafür sein, da die Röhren mit Zsp. und gealtertem Oxalatplasma fast dieselbe Ger.zeit bieten wie mit frischem Oxalatplasma. Im Plasma dürfte der alternde Stoff das Prothrombin sein, und es könnte ja dann die Erscheinung so erklärt werden, dass das Prothrombin des frischen Liquors jenes gealterte im Plasma ersetzt. Wieso aber sieht man in der Zsp. ein Altern des Prothrombins nur in geringem Masse? Freilich in Tab. 12 werden zwar verschiedenen alte Zsp. angeführt, aber frisches Plasma, das ja genügend reaktionsfähiges Prothrombin enthält. Doch sehen wir oft, wenn wie ältere Zsp. und älteres Plasma zusammenbringen doch sehr kurze Ger.zeiten z.B. Pr. Nr. 132: am 27—12—43 zeigt eine Zsp., die 6 Tage alt ist mit einem Oxalatplasma, das 7 Tage alt ist, eine Ger.zeit von 11' während die Recalcifizierungszeit ca 101' ist! In der Zsp. muss also ein Faktor enthalten sein, der das Prothrombin frisch erhält. Die obigen Versuch sprechen aber sonst auch für das Vorkommen von Prothrombin in der Zsp.

Bevor wir eine weitere Klärung der eben besprochenen Fragen versuchen, sei noch einmal der *chemischen Natur der Thrombokinase* gedacht. Sie ist nicht vollständig entschieden, denn noch heute gibt es Forscher, die von Lipoidciweisskomplex sprechen. Doch die meisten Autoren nehmen an, das es sich hierbei um Phosphatide handelt. Seit Howell's und seiner Schüler Arbeiten wird die thromboplastische Substanz, wie Howell die Thrombokinase bezeichnet, auf Grund ihrer chemischen Eigenschaften als Kephalin aufgefasst. Dieses ist ja auch der einzige Ger.aktive Stoff der Phosphatidgruppe, da weder Lecithin, noch Cholesterin, Lysolecithin, Heparphosphatid und Sphingomyelin eine solche Wirkung erkennen lassen. Nun werden nach den Untersuchungen von Seuberling (43) 0.03 mg %, nach jenen von Roeder (41) 0.04 mg % als obere Grenzzahlen für den normale Lumballiquor angenommen. Seuberlings Werte für die 3 Kategorien der Zsp. sind: Lumballiquor 0.02—0.03 mg %,

Cysternenliquor 0.012—0.024 mg %, Ventrikelliquor 0.05—0.012 mg %. Pathologischer Ventrikelliquor wurde, soweit ich sehe, nur in einem Fall von Dermoidcyste untersucht, wobei in ihrem 0.068 mg %, im suboccipitalen Liquor 0.06 mg % Phosphatide nachzuweisen waren. In Fällen von Hydrocephalus hat Seuberling im Cysternenliquor als Höchstwert 0.03 mg % gefunden. Eine weitere Differenzierung hat m.W. bisher nicht stattgefunden. Man kann und darf daher nicht viel über den Zusammenhang der genannten Zahlen mit den die Ger. aktivierenden Faktoren sagen. Das natürlich schon sehr geringe Mengen zu solchen Funktionen befähigt sein können, ist nicht von der Hand zu weisen. Haben doch Gratia und Levene (26) gezeigt, dass Kephalin noch in der Verdünnung  $5^{-7}$  erheblich Ger. beschleunigend wirkt. Innerhalb der obengenannten Zahlen können die verschiedenen Phosphatide im verschiedenen Verhältnis vertreten sein, so dass die starke Ger. aktivität des Ventrikelliquors bei Hydrocephalus nicht ganz unerklärlich zu sein braucht im Hinblick auf die Seuberling'schen Werte. Immerhin ist es auffallend, dass des Phosphatidgehalt nach Seuberling (43) vom Ventrikel- zum Lumballiquor zunimmt, also die Stoffe während der Zirkulation der Zsp. aus dem Gehirnstoffwechsel wohl aufgenommen werden, während wir annehmen müssen, dass zu mindestens ein Teil der Ger. aktiven Stoffe der Zsp. gleich bei ihrer Sekretion zugeteilt werden. Dafür spricht der stark Ger. aktive Ventrikelliquor bei Hydrocephalus (s. S. 21). Auffallend war ja auch, dass wir bei Verwendung von Oxalatplasma Werte gefunden, die einander im allgemeinen ziemlich nahestanden und vom Eiweissgehalt unabhängig waren. Die chemischen Untersuchungen von Seuberling (43) zeigen aber einen ziemlich weitgehenden Parallelismus zwischen Eiweiss- und Phosphatidgehalt. Freilich beklagt sich Roeder (41) darüber, dass der Phosphatidgehalt der Zsp. nicht parallel geht der Schwere der Abbauerscheinungen im Zentralnervensystem. Die relativ hohen Werte, die sich bei Rückenmarkstumoren fanden (1.3 mg %) erklärt Roeder (41) als durch Permeabilitätserhöhung aus dem Blut stammend. Es besteht jedenfalls ein Kontrast zwischen der starken Ger. aktivität der Zsp. und dem niedrigen Phosphatidgehalt, was freilich nach den erwähnten Untersuchungen von Gratia und Levene (26) durchaus erklärlich ist. Klarheit werden wir hier erst bekommen, wenn wir genaue Methoden zur Bestimmung der ver-

schiedenen Phosphatide haben und auch die Ger. faktoren in der Zsp. genauer kennen. Dann werden wir auch sagen können, ob die betreffenden Ger. faktoren *aus dem Blute stammen oder liquor-eigen* sind bezw. dem Stoffwechsel des Zentralnervensystems entspringen. Nach dieser Richtung hin wäre auf Grund unserer bisherigen Versuche nur wenig zu sagen. Wir hatten von vornherein angenommen, dass bei der Paralyse, wo die Permeabilität erhöht ist, so dass haemolytische Normalambozeptoren aus dem Blut in die Zsp. eindringen [Weil und Kafka (46)], auch Ger. aktive Stoffe aus dem Blute übertreten können. Dafür scheinen nun die Versuche mit Magnesiumsulfatplasma zu sprechen, aus denen hervorgeht, dass in erster Linie Paralysen in ihrer Zsp. nachweisbare Ger. aktive Stoffe enthalten. Das schwache Reagieren des Magnesiumsulfatplasmas wird ja meist darauf zurückgeführt dass durch die starke Salzkonzentration (28 %) die Wirkung des im Plasma enthaltenen Prothrombins gehemmt wird. Es wäre also, wenn Prothrombin aus dem Blut infolge der Permeabilitätserrhöhung in die Zsp. übertritt, das Erscheinen der Ger. verständlich. Wir wollen hier absehen von der Annahme von Fuchs, dass das Prothrombin im strömenden Blut nicht vorhanden ist, und die Ansicht der anderen Autoren, dass er der Fall ist, als gegeben ansehen. Leider hatten wir nur wenige Paralysenfälle zur Untersuchung und diese waren mit Malaria behandelt mit demgemäss abgeschwächtem Befund der Zsp. Zwei Versuche sprechen vielleicht im oben angedeuteten Sinne. In dem einen Fall handelte es sich um die Zsp. einer mir Malaria behandelten Paralyse. 3 cm<sup>3</sup> dieser Zsp. zeigten, bei Zimmertemperatur mit Magnesiumsulfatplasma untersucht, eine stärkere Ger., wenn das Plasma verdünnt war. Ferner sei eines Falles gedacht, des schon früher erwähnt worden ist. Es handelte sich um eine malariabehandelte Paralyse, die in der Zsp. den Globulinalbuminquotienten 1.6 (stark erhöht) hatte. Hier zeigte, die mit Äther vorbehandelte Zsp. eine Ger. zeit von 15', die native von 27'. Dieselbe Zsp. war 3 Monate vorher untersucht worden; damals hatte die native. Zsp. die Ger. zeit 30', also ähnlich, wie beim zweiten Versuche, die mit tertiärem Calciumphosphat adsorbierte eine solche von Stunden. Der mit Äther eluierte Calciumphosphatrückstand wies im Eluat, das nach Ätherverdunstung in 0.9 %iger NaCl-Lösung aufgenommen worden war, nach Beschiekung mit CaCl<sub>2</sub> eine Gerinnungsbeschleunigung gegenüber



der Recalcifizierungskontrolle auf. Andere Versuche mit der Zsp. von Paralyse und bei Verwendung von Oxalatplasma zeigten keine wesentlichen Unterschiede gegenüber andersartigen Fällen, sowohl was die Ger. zeit der nativen Zsp. betrifft, als auch in bezug auf die Resultate der mit Äther geschüttelten Zsp. Bevor wir hier zu richtigen Deutungen gelangen, müssen eingehende Analysen nach Art der geschilderten Beispiele ausgeführt werden usw. an Zsp. unbehandelter frischer Paralyse vorgenommen werden. Leider steht mir ein solches Material derzeit nicht zu Verfügung. Es ist daher vorläufig nur die Möglichkeit nicht auszuschliessen, dass bei der *Paralyse das Prothrombin in der Zsp. vermehrt* sein kann. Freilich scheint, wie wir schon ausgeführt haben, es so zu sein, dass in der Zsp. auch Thrombokinasen durch tertiäres Calciumphosphat adsorbiert wird.

Wir müssen uns schliesslich noch fragen, ob wir durch unsere Versuche etwas zur *Theorie der Ger.* beigetragen haben. Nach der alten von Alexander Schmidt begründeten und von Morawitz (38), Fuld (24) und Gross, Bordet (4), Howell (27), Wöhlisch (49, 50) u.a.v. weiter geführten Ger. theorie stellt sich bekanntlich der Ger. vorgang so dar, dass in der ersten Phase der Ger. das im Plasma vorhandene Prothrombin oder Thrombogen oder Serozym mit der aus Blut- oder Gewebszellen stammenden Thrombokinasen oder Cytozym in der Anwesenheit von Calciumionen zum Fibrinferment oder Thrombin zusammentreten. Das ist die erste Phase der Ger. In der zweiten Phase wirkt das Thrombin auf das Fibrinogen ein und wandelt es zu Fibrin um. In der dritten Phase retrahiert sich das Fibringerinnsel unter der Einwirkung von Stoffen, die aus den Blutplättchen stammen. An diesem Gerüst der Ger. vorganges muss man auch heute festhalten, trotzdem in einer Unzahl von interessanten Arbeiten nicht nur verschiedene Namen für die einzelnen Faktoren eingeführt worden sind, sondern auch die einzelnen Vorgänge verschiedenartig dargestellt werden. So wird in der Litteratur darüber diskutiert, ob es sich bei der Ger. um rein fermentative oder mehr kolloidchemische Vorgänge handelt, ferner darüber, ob die Calcium- oder Thrombokinasewirkung einen spezifischen Vorgang darstellt oder bei Faktoren durch andere Stoffe ersetzbar sind. Hier sei nur zur Illustration des Gesagten erwähnt, dass Dyckerhoff und seine Mitarbeiter der Annahme sind, dass im Blute das Thrombin mit einem Hemmungskörper zusammenge-

koppelt ist, und erst durch das Zusammentreten mit der Thrombokinase wird dieser Hemmungskörper ausgeschaltet und das Thrombin kommt zur Wirkung. Diese Ausschaltung des Hemmungskörpers soll unspezifisch sein. Das Thrombin wandelt das Fibrinogen in Fibrin um, es denaturiert das Fibrinogen, weswegen das Thrombin als Denaturase bezeichnet wird [Wöhlisch (49, 50)]. Wir können an dieser Stelle natürlich nicht auf andere Ger. theorien eingehen. Für unsere Darstellung genügt es zu betonen, das zur Ger. im allgemeinen 4 Stoffe notwendig: einer der sich im Blutplasma gelöst vorfindet (Prothrombin, Thrombogen, Serozym), ein anderer, der den Blutzellen und Plättchen oder Organzellen entstammt (Thrombokinase, thromboplastische Stoffe, Cytozym, Ger. aktive Zellstoffe), schliesslich Calciumionen und das Fibrinogen. In dem bei der Ger. abgetrennten Serum sind das Thrombin, ferner zu einem kleineren Teile seine Vorstufe, das Prothrombin, und Calciumionen enthalten.

Bezüglich *anderer Körperflüssigkeiten* wäre zu erwähnen, das schon Buchanan (7) gezeigt hat, das Transsudate und zwar ganz besonders Hydroceelenflüssigkeit keine Neigung besitzen, spontan zu gerinnen, sondern erst nach Hinzufügung eines »Reagens«, das im Blute vorhanden ist. Auch A. Schmidt ist bei seinen berühmten Untersuchungen von ähnlichen Beobachtungen ausgegangen. Fonio (20) betont in seinem grossen Referat, dass menschliche Transsudate oft reine Fibrinogenlösungen darstellen, die frei von Thrombin und seinen Vorstufen sein können; solche Flüssigkeiten gerinnen nicht auf Zusatz von Thrombokinase oder von Kalksalzen allein, sondern erst auf Hinzufügung von Serum. Nicht alle Transsudate verhalten sich so. Vielfach sind ihnen Vorstufen des Thrombins beigemischt und in solchen Fällen genügt ein Zusatz der anderen d. h. der fehlenden Vorstufe, um Thrombin zu bilden und damit die Ger. auszulösen. Ein Teil dieser Transsudate gerinnt ferner spontan infolge des Gehaltes an Thrombin oder allen seinen Vorstufen. Häufig sind jene Transsudate, die nur Fibrinogen enthalten. Eine solche Lösung ist der beste Indikator für Thrombin. Dazu eignet sich ganz besonders das perikardiale Exsudat des Pferdes. Die normale Zsp. unterscheidet sich schon von allen diesen Flüssigkeiten dadurch, dass sie kein Fibrinogen enthält. Sie enthält dagegen Thrombokinase und wahrscheinlich etwas Prothrombin, ein Verhalten, das dieser Flüssigkeit einen besonderen Platz

innerhalb der Körperflüssigkeiten zuweist und die Zsp. in die Nähe gewisser Organzellen (z.B. Blutplättchen) oder ihrer Extrakte bringt, die ebenfalls beide Vorstufen, aber kein Fibrinogen enthalten. Es wäre von Interesse festzustellen, ob die Flüssigkeit der vorderen Augenkammer sich auch in dieser Richtung ähnlich verhält wie die Zsp.

Die Ger.forschung wird also durch unsere Untersuchungen insofern gefördert, als es nun wohl feststeht, dass es Körperflüssigkeiten gibt, die sich insofern wie Gewebssäfte verhalten, dass sie kein Fibrinogen, dagegen beide Vorstufen der Thrombins enthalten. Vielleicht kommen auch beide hier in Modifikationen vor in denen sie nicht so scharf abgegrenzt sind wie im Blute, wodurch vielleicht einige unserer Ergebnisse eine Erklärung finden würden z.B. die ev. Adsorption der Thrombokinese durch tertiäres Calciumphosphat. in der Zsp.

Wenn sich also in dieser Arbeit noch nicht alle Fragen klären liessen, so möchten wir daran erinnern, dass auch in den Ger.fragen, die das Blut selbst betreffen, trotz einer Unzahl ausgezeichneten Arbeiten noch so viele grosse Differenzen bestehen. Um nur eines noch einmal zu nennen: Wir haben gehört, dass Dyckerhoff und seine Mitarbeiter angenommen haben dass das Thrombin im strömenden Blut durch einen Inhibitor in seiner Wirksamkeit gehemmt wird; dieser Inhibitor wird durch die Thrombokinese aufgehoben, so dass das Thrombin nicht zur Ausübung seiner Funktion kommt. Also kein Wort von der Vorstufe des Thrombins, dem Prothrombin. Blicken wir zurück in der Geschichte der Ger.forschung, so sehen wir, dass A. Schmidt der Auffassung war, dass im strömenden Blut ein Cytoglobin die Wirkung des Prothrombins hemmt. Dagegen hat Bordet angenommen, dass im Blute das Proserozym vorhanden sei, ein maskiertes Prothrombin. Howell wiederum hat angenommen, dass im strömenden Blute zwar Prothrombin vorhanden sei, dass es aber durch ein Antithrombin gehemmt wird. Und Fuchs wiederum bestreitet das Vorkommen von freiem Prothrombin im strömenden Blute, da es durch ein Antithrombin maskiert wird. Die Anschauungen schwanken also von der Annahme eines Prothrombins über ein maskiertes Prothrombin bis zur Leugnung eines Prothrombins im strömenden Blute! Diese Fragen bedürfen erst endgiltiger Klärung. Es dürfte aber trotzdem nicht zuviel gesagt sein, wenn wir behaupten,

dass die weitere Erforschung der Zsp. auf Ger. aktive Stoffe nicht ohne Vorteil für die Klarlegung mancher heute noch sehr verworrenen Begriffe der Ger.forschung sein wird. Wir hoffen jedenfalls in weiteren Mitteilungen Beiträge dazu liefern zu können.

*Wir kommen zu folgenden Schlüssen:*

1) Die normale Zsp. ist in allen ihren Kategorien (Lumbal-, Cysternen- und Ventrikelliquor) Ger. aktiv. Die letztgenannte Flüssigkeit scheint es sogar am stärksten zu sein. Als Ger. zahl der Zsp. möchte ich die Ger. zeit bezeichnen, die 1.5 cm<sup>3</sup> Zsp. an 0.1 cm<sup>3</sup> frischen normalen Oxalatplasmas bei 37° bewirkt. Sie ist im Mittel  $22' \pm 6' 24''$  für die Lumbal- und Cysternenflüssigkeit bei Brutschranktemperatur. Nähere statistische Angaben erfolgen in der nächsten Mitteilung.

2) Die Ger.aktivität der Zsp. ist nicht etwa eine Funktion des Ca-Gehaltes, der freilich massgebend mitwirkt, sondern es ist nachzuweisen, dass die fibrinogenfreie Zsp. Thrombokinase und in geringen Masse Prothrombin enthält. Letzterer Stoff scheint bei noch liquorpositiven Paralysen erhöht zu sein. Durch die Adsorption nach Bordet dürfte in der eiweissarmen Zsp. auch Thrombokinase mitgerissen werden.

3) Die Ger.wirkung auf Oxalatplasma ist unabhängig vom Eiweissgehalt der Zsp., sonstigem Liquorbefund und Diagnose, während bei der Einwirkung auf Magnesiumsulfatplasma, die relativ selten auftritt, Paralysen, Fälle von Lues cerebri und solche mit erhöhtem Eiweissgehalt bevorzugt erscheinen.

4) Die Ger. aktiven Stoffe dürften der Zsp. zum Teil schon bei der Entstehung beigemischt zu sein. In welchem Masse sie dem Gehirnstoffwechsel oder dem Blute entstammen, müssen weitere Untersuchungen ergeben.

5) Die Ergebnisse scheinen dafür zu sprechen, dass in fibrinogenfreien Flüssigkeiten Thrombokinase und Prothrombin nebeneinander existieren können und dass sie in der Zsp. vielleicht nicht so streng abgrenzbar sind wie in anderen Körperflüssigkeiten. Die erwähnte Besonderheit stellt die Zsp. biologisch in die Nähe der Gewebsflüssigkeiten.

6) Auf Grund dessen, dass die normale Zsp. das Komplementmittelstück ohne die sonst im Blute dazu gehörigen Labilglobuline enthält, scheint es notwendig zu sein, die von Fuchs und seinen

Mitarbeitern angenommenen Beziehungen von Ger. faktoren (Prothrombin) zu immunbiologisch charakterisierten Körpern (Mittelstück des Komplements) mit der Zsp. wiederaufzunehmen, zumal hier auch das Prothrombin ohne den dazu gehörigen Eiweisskörper vorzukommen scheint.

### Litteratur.

- 1) Abramson, L.: De la teneur du liquide cérébrospinal humain en sodium etc. Lund 1930. — 2) Astrup, T.: Bioch. Zeitschr. 313, 229 (1942/43). — 3) Behrendt: Bioch. Zeitschr. 144 (1924). — 4) Bordet: Annal. inst. Pasteur, 34, 561 (1920). — 5) Bordet et Gengou: Annal. inst. Pasteur, 15, 129 (1901) u. 17, 822 (1901). — 6) Brock: Bioch. Zeitschr. 10, 140/141, 591 (1923). — 7) Buchanan: On the coagulation of blood. Phil. soc. Glasgow (1844—1848. — 8) Dale u. Walpole: Bioch. J. 10, 331, 1916. — 9) Dyckerhoff u. Marx: Bioch. Zschr. 313, 107 (1942). — 10) Dyckerhoff, H. Glamser u. K. Widmann: Bioch. Zschr. 314, 250 (1943). — Dyckerhoff u. Deschler, Bioch. Zschr. 314, 258 (1943). — 12) Dyckerhoff, Steiner u. Miehler: Bioch. Zschr. 297, 1 (1938). — 13) Dyckerhoff, Miehler und Steiner: Bioch. Zeitschr., 297, 342 (1938). — 14) Dyckerhoff u. Goossens: Bioch. Zschr. 299, 437 (1938). — 15) Dyckerhoff, v. Behn, Goossens u. Miehler, Bioch. Zschr. 288, 271 (1936). — 16) Dyckerhoff: Über die Gerinnung des Blutes. Hdb. d. Enzymologie I 632 (1940). — 17) Eagle und Harris: J. gen. Physiol. 20, 545 (1937). — 18) Eskuchen: Die Lumbalpunktion, Berlin—Wien 1919. — 19) Ferguson, John H.: Blod. Annual Rev. of Physiol. Vol. II (1940). — 20) Fonio: Die Gerinnung des Blutes. Hdb. der norm. u. path. Physiolog. 6<sup>I</sup>, 307 (1928). — 21) Fuchs, Hans J.: Die Rolle des Prothrombins bei der Blutgerinnung. Erg. der inn. Med. 38, 173 (1930). — 22) Fuchs, Hans J.: Zschr. f. Immf. 62, 117 (1929) u. 62, 107 (1920). — 23) Fuchs, Hans J. Falkenhausen und Hartmann: Zschr. f. d. ges. exp. Med. 64, 227 (1929). — 24) Fuld: Zentrbl. f. Phys. 19 (1903). — 25) Goeckel: Zschr. f. d. ges. Nehr. u. Psych. 79, 303 (1922). — 26) Gratia und Levene: J. of biolog. Chem. 50, 455 (1922). — 27) Howell: Americ. J. of Physiol. 26, 453 (1910), 34, 692 (1913), 35, 474 (1914). — 28) Jorpes, J. Erik: Heparin. Hygiea 100, 256 (1938). — 29) Kafka, V.: Klin. Wschr. 1, 2527 (1922). — 30) Kafka, V.: Die Zerebrospinalflüssigkeit. Leipzig u. Wien 1930. — 31) Kraus und Fuchs: Zschr. f. exper. Med. 64, 583 (1929) u. 65, 245 (1929). — 32) Kürten und Harzer: Zschr. f. exper. Med. 102, 449 (1937). — 33) Lehmann, J.: Nordisk Medicin, 12, 3192 (1941). — 34) Lehmann, J.: Svenska läkartidn. 1942, nr. 37. — 35) Lesourd u. Pagniez: Cr. Soc. Biol. Paris, 62, 934 (1907). — 36) Marrack-Thacker: The biochem. journ. 20, 580 (1926). — 37) Mellanby und Pratt: J. of Physiol. 92, 5 (1938). — 38) Morawitz: Arch. f. klin. Med. 79, 1 u. 25 (1904). — 39) Neufeld, L.: Zschr. f. Immf. 26, 368 (1917). — 40) Quick: The journ. of immun. 29, 87 (1935). — 41) Roeder: Z. f. d. ges. Neur. u. Psych. 168, 519 (1940).

- 42) Schmidt, A.: Zur Blutlehre, Leipzig 1892. — 43) Seuberling: Z. f. d. ges. Neur. u. Psych. 158, (1937). — 44) Sary, Kral und Winternitz: Z. f. d. ges. exp. Med. 66, 671 (1929). — 45) Thierfelder und Klenk: Die Chemie der Phosphatide. — 46) Weil und Kafka: Wien. Kl. Wschr. 26, 10 (1911). — 47) Weitnauer und Wöhlisch: Biochem. Z. 288, 137 (1936). — 48) Wising: Acta med. scand. 94, 506 (1936). — 49) Wöhlisch, E.: Die Physiologie und Pathologie der Blutgerinnung. Erg. der Physiol. 28, 443 (1929). — 50) Wöhlisch, E.: Thrombose und Blutgerinnung. Die Methoden der Ferment f. 3, 2110 (1941). — 51) Wöhlisch, E. und L. Juhling: Biochem. Z. 297, 353 (1938). — 52) Wöhlisch, E., W. Diebold u. O. Kiderlen: Pflügers Arch. 237, 599 (1936).
-



## Ouvrages envoyés aux *Acta medica scandinavica*.

*The Medical Annual 1944*: 404 p., 44 fig., XL plates. Wright,  
Bristol, London 1944.

---





(From the Laboratory for Medical Chemistry, The Medical Department,  
The Carolinian Hospital (Karolinska Sjukhuset), Stockholm.)

## The Kidney Function and the Renal Clearances of some Sulfanil-amide derivatives.<sup>1</sup>

By

OLOV LINDAHL and BERTIL JOSEPHSON.

(Submitted for publication August 30, 1944).

---

If one wishes to study the excretion of the sulfanil-amide derivatives through the kidneys one can content oneself with determining the amount recovered in the urine. Numerous investigations on the recovery in proportion to the amount administered have been published in respect of a great many of these compounds. But these investigations do not throw any light on the mechanism for the excretion, or on the influence of the latter on the distribution of free and acetylated sulfanil-amides.

A better insight into these conditions can be got by studying the renal clearances of the substances in question. Several such investigations have recently been published (Taylor, Lowell, Adams, Spring, Finland 1940, Reinhold, Flippin, Schwartz, Domini 1941, Strauss, Lowell, Taylor, Finland 1941, Frisk 1941 and 1943). If one is to draw further conclusions from clearance experiments, however, one must be able to compare the clearance-values obtained with the real glomerulus filtration, i. e. with a clearance by which the filtration can be estimated with some degree of certainty. Of the investigators mentioned above only Frisk has taken account

---

<sup>1</sup> This investigation has been aided by grants from the foundations »Konung Gustaf V:s 80-årsfond» and »Thérèse och Johan Anderssons Minne».

of this possibility by determining the creatinine clearance simultaneously with the clearance of the sulfanil-amides under investigation. But the creatinine clearance cannot be regarded as a satisfactory standard for the glomerular filtration, since the investigations of Shannon (1935) have shown that the creatinine is not only filtered by the glomeruli but also excreted by the tubuli. (According to Miller and Winkler, 1938, this is not the case when no extra creatinine is given.) According to Homer Smith, the inulin clearance is a much truer measure of the filtration in man. This statement, however, has been subject to criticism (Ekehorn 1944), and the question as to which clearance gives the most accurate picture of glomerular filtration should perhaps not be regarded as definitely solved. In the experiments reported here we have chosen the inulin excretion as standard clearance mainly because for many reasons we consider it probable that this clearance in a better way than others corresponds to the glomerular filtration. At present, moreover, inulin is considerably cheaper than the rather expensive creatinine. In some cases, however, we have carried out both the inulin and the creatinine clearances simultaneously with the sulfa-clearance.

Everybody who has worked with clearance determinations in man is familiar with the fact that these determinations are sometimes subject to considerable experimental errors, even when carried out with great care. A clearance determination, continued during one period only, is thus of very limited value. None of the investigators mentioned above, however, seems to have continued the clearance determinations during more than one period. In the experiments reported in the present paper nearly all the clearance determinations were carried out during two, or sometimes three, consecutive periods of about one hour each. Moreover, the results of the double or triple experiments thus performed have not been included here if they showed a divergence in the clearance values for inulin or free sulfa-compound of more than 20 % between the values found in the different periods and their mean value. In an earlier paper (Josephson and Lindahl 1943) we have drawn attention to the fact that inulin clearance during the 4th hour after injection of the inulin is frequently (with statistically established difference) lower than it is during the 2nd and 3rd hours. By discarding experiments with greater divergence than 20 % between

the clearance values we have excluded divergences of this and other kinds.

As it thus seemed to us that the excretion mechanism of the sulfanil-amides had not been satisfactorily investigated, we found it worth while to examine their plasma-renal clearance with reliable methods and to make a comparison with simultaneously performed inulin clearance. In this connection we determined both free and acetylated sulfanil-amides. We also made attempts to calculate the back resorption of these substances in the tubuli or alternatively to ascertain what proportion of the sulfanil-amides occurring in the blood-plasma is filtered in the glomeruli.

### *Methods.*

The subjects were all bed-patients in the medical and surgical departments of the hospital. For each of the preparations tested a number of patients were selected who did not show any signs of impairment of the kidneys and whose heart and circulation were normal. Further, each preparation was tested out on a number of patients with clear evidence of kidney disease having a marked influence on the renal function, especially the glomerular filtration.

The subjects were given the sulfanil-amide to be tested in doses of varying magnitude, in order to obtain varying plasma concentrations. The doses were administered orally, as in this way the plasma concentration values remain more or less constant for a length of time sufficient to allow the clearance determinations to be made. In no case did we observe any trouble in the kidneys or urinary tract caused by the medicament. This also applies to the cases with renal disorders. In some cases the preparations were administered continuously for therapeutic reasons — e.g. for wound infections, otitis, etc. In other cases, in which the treatment was not otherwise called for, the doses were administered only the day before and the same day as the clearance test was carried out. No patients suffering from diabetes were used, as hyperglycemia makes the inulin determinations unreliable.

The inulin test was carried out according to Alving and Miller (1940), with a single intravenous injection of about 100 ml of a 10 % inulin solution.<sup>1</sup> When the creatinine clearance was to be

<sup>1</sup> Ampullas of inulin solution from A/B Astra, Södertälje, Sweden, were employed. This was identical with the preparation II mentioned in an earlier paper (Josephson and Lindahl 1943).

determined the patients were given 3 g of pure creatinine orally at the same time as the inulin. The clearance determination was started from 45 to 60 minutes after the injection, and was carried on for two or three consecutive periods, usually of 60 minutes each. Blood samples were taken in the middle of each period, and with a few exceptions the urine was collected by catheter, which was kept in position during the whole experiment. The inulin concentrations were determined according to Corcoran and Page (1939), with the modification that the treatment with yeast was omitted, as this had proved to give more correct values (Josephson and Lindahl 1943). The creatinine analyses were carried out according to Liebs' and Zackerls' (1934) modification of the Rehberg method. The sulfanil-amides were determined by Marshall's (1937) method as modified by Hecht (1938) and carried out by Frisk (1943). Unlike Frisk, who preferred coupling with N-ethyl-2-naphthyl-amine, we employed N-ethyl-1-naphthyl-amine. We have found that the latter amine gives a stronger colour than the former and of a somewhat different wave-length. The colour was read in a step-photometer of Pulfrich. (No N-1-naphthyl-ethylenediamine-dihydro-chloride for the method of Bratton and Marshall (1939) was available in Sweden when this investigation was carried out.) The concentrations were calculated by comparison with standard solutions prepared by dissolving the sulfanil-amide in question in human plasma. At least three such solutions were used for each preparation. Unlike Frisk (1943), we employed separate standards prepared in the same way also for the N-acetyl derivatives. All analyses of plasma standards were carried out on heparin plasma. The samples from the subjects were usually oxalated plasma with a minimum of lithium oxalate. In some cases heparin was used instead of the oxalate. In a number of comparative experiments we have found identical values of sulfanil-amide concentration in plasma from heparin blood and oxalate blood where both have been taken at the same time from the same patient. The sulfanil-amide standards for the determinations in the urine were dissolved in water. The substances used for the standard solutions were of the highest available purity with controlled melting-points. The preparations administered orally were commercial tablets. In this connection we wish to express our thanks to the factories A/B Astra, Södertälje, H. Lundbeck & Co., Malmö and A/B Pharma-

cia, Stockholm, that kindly provided us with the sulfanil-amides and the acetyl derivatives.

The clearance values have been calculated according to the usual formula: clearance ml/min. =  $\frac{V \times Cu}{Cp \times t}$ , where V = urine volume, Cu = concentration in the urine, Cp = concentration in the plasma, t = test-time in minutes

In the column «Apparently back-resorbed» in the tables is to be found the amount per cent of the filtered substance that has been resorbed again. It has been calculated on the assumption that all the determinable sulfanil-amide in the plasma is filterable to the same extent and at the same rate as inulin. This «back-resorption» has been calculated according to the formula: % back-resorbed =  $100 \frac{Cl_I - Cl_S}{Cl_I}$ , where  $Cl_I$  = inulin clearance and  $Cl_S$  = clearance of the sulfa-preparation under investigation. In the column «Apparently filterable part» is to be found the percentage of sulfa-preparation that would, as in the case of inulin, be freely filterable in the glomeruli on condition that a part of the same preparation in the plasma is in a non-filterable form, and that neither excretion nor resorption of the preparation in question occurs in the tubuli. The filterable part has been calculated according to the formula: per cent filterable =  $100 \frac{Cl_S}{Cl_I}$  or = 100 — percentage back-resorbed. In the cases in which sulfanil-amido-methyl-thiodiazole was administered no values for resorption or excretion are given for reasons which will be made clear later in this paper.

### Results.

Cases where the average difference between the mean value of the case and the values found in the different periods for the clearances of inulin or free sulfa-compound was above 20 per cent have not been included in our tables and calculations. The clearance values from the acetylated compounds, however, have been made exceptions from this condition, as their determination is based on the difference between the concentration of the total and free compounds. These values must necessarily show very heavy experimental errors. Consequently no results have been excluded only on account of poor agreement in the clearance of the acetylated sulfa-compounds.

Our clearance values for the free compounds (tables 1, 2, 3, 5) are in fairly close agreement with those obtained by earlier investigators, at least, if one takes into consideration the great dispersion attaching to these results. The clearance for the acetyl compounds, on the other hand, we have found in most cases to be lower than that given by Reinhold, Flippin, Schwartz and Domm (1941) and by Frisk (1941). In the case of sulfa-thiazole this difference is considerable, as unlike earlier investigators we usually found the clearance of the acetyl-sulfathiazole to be considerably lower than that of the free compound. In our material this difference could be statistically proved. This discrepancy is too great to be explained by the fact that these investigators do not seem to have used standard solutions made up of N-acetyl derivatives in plasma for the calculation of the concentration of the acetylated compounds. We have tried to obtain confirmation of the correctness of the low clearance values for acetyl-sulfa-thiazole found by us in the following way: In 3 cases (table 4) we gave the patients only the acetyl compound by mouth, afterwards determining its clearance. (In these 4 cases, however, the clearance values were only approximative, as the acetyl-sulfa-thiazole is resorbed to such a low degree that the concentration in plasma and urine can not be exactly determined.) Since the sulfa-methyl-thiodiazole is acetylated only to a slight degree in the organism, we determined also the clearance of this acetyl compound by giving the subjects only the pure acetyl derivative. (Table 6).

### Discussion.<sup>1</sup>

#### I. *Sulfanil-amide, sulfa-pyridine, sulfa-thiazole.*

All our clearance calculations are based on the assumption that no acetylation of the sulfanil-amides worth mentioning takes place in the kidneys. If they are acetylated during the passage through the blood vessels of the kidneys, during the filtration or in the tubuli, then of course, the whole basis of the clearance calculations becomes erroneous. A more or less analogous process to this acetylation is the benzoylization of glycine in connection with the formation of hippuric acid, which has been shown to be able to take

<sup>1</sup> In carrying out the statistical calculations reported in this paper we have been assisted in a very valuable way by Dr. E. v. Hofsten of the Statistical Office of the City of Stockholm. We owe him much gratitude for his assistance.

Table 1.  
Sulfa-thiazole.

Case No.	Body surface area m <sup>2</sup>	Period minutes	Urine ml	Inulin-clearance ml/min.	Free sulfa-thiazole				Acetyl-sulfa-thiazole				Diagnoses
					Plasma conc. mg/100 ml	Clearance	Apparently back-re-sorbed % of filtered	Apparently filterable part % of total	Plasma conc. mg/100 ml	Clearance	Apparently back-re-sorbed % of filtered	Apparently filterable part % of total	
1	1.85	75	69	113	11.6	49	56	44	3.1	15	86	14	Normal case
		50	38	106	10.0	50	53	47	3.1	23	80	20	
		60	67	97	10.0	43	56	44	2.3	66	35	65	
2	1.85	60	125	143	8.5	60	58	42	3.8	6	96	4	"
		62	410	133	8.5	51	62	38	3.8	15	89	11	
		58	145	132	6.2	56	58	42	5.4	9	94	6	
3	1.60	60	60	121	7.7	45	63	37	5.4	15	88	12	"
		60	60	183	7.7	45	73	27	5.4	19	90	10	
		60	60	127	6.9	46	64	36	4.6	18	86	14	
4	—	59	130	137	9.2	52	62	38	6.9	10	93	7	"
		59	132	105	7.7	59	44	56	5.4	8	92	8	
		59	138	113	7.7	53	53	47	5.4	13	89	11	
5	1.78	57	60	108	7.7	35	68	32	5.0	11	90	10	"
		59	70	122	6.9	45	63	37	3.1	39	68	32	
		60	205	122	6.2	43	65	35	3.9	25	79	21	
6	1.95	58	40	156	7.2	77	51	49	3.6	14	91	9	"
		60	255	182	6.9	67	62	38	4.6	0	100	0	
7	1.94	61	148	116	5.4	40	65	35	2.3	21	82	18	"
		60	385	149	3.9	54	64	36	2.7	20	87	13	
8	1.80	58	80	166	9.2	49	70	30	2.3	35	79	21	"
		61	170	115	8.5	58	50	50	4.6	0	100	0	
		59	190	154	6.9	74	52	48	6.2	14	91	9	
9	1.80	59	460	129	3.1	67	48	52	3.1	42	68	32	"
		60	410	122	3.1	61	50	50	3.1	37	70	30	
		60	370	104	3.1	55	47	53	3.1	14	86	14	
10	1.94	59	220	160	7.7	53	67	33	5.4	0	100	0	"
		65	510	133	6.2	62	53	47	3.8	0	100	0	
		55	330	133	6.2	65	51	49	3.8	0	100	0	
11	1.96	58	50	133	2.3	57	62	38	1.5	0	100	0	"
		61	65	137	2.3	52	57	43	1.5	9	92	8	



Case No.	Body surface area m <sup>2</sup>	Period minutes	Urine ml	Inulin-clearance ml/min.	Free sulfa-thiazole				Acetyl-sulfa-thiazole				Diagnoses
					Plasma conc. mg/100 ml	Clearance.	Apparently back-re-sorbed % of filtered	Apparently filterable part % of total	Plasma-conc. mg/100 ml	Clearance	Apparently back-re-sorbed % of filtered	Apparently filterable part % of total	
12	1.81	64	665	157	5.8	66	58	42	4.2	40	75	25	Normal case
		59	179	128	5.8	42	67	33	4.2	27	85	15	
		60	315	176	3.9	53	72	28	4.6	30	95	5	
13	1.81	62	260	131	3.1	47	64	36	1.5	49	63	37	,
		61	482	160	3.1	56	65	35	1.5	0	100	0	
		60	483	125	3.1	42	67	33	0.8	87	31	69	
14	1.82	60	679	122	9.0	66	46	54	3.4	32	73	27	,
		58	322	126	8.5	62	51	49	2.3	33	75	25	
15	1.85	60	56	140	5.5	51	64	36	2.3	38	61	49	,
		60	71	127	6.0	44	65	35	2.3	51	50	50	
16	1.90	58	520	161	4.2	54	67	33	2.2	68	58	42	,
		65	582	150	3.8	56	63	37	2.2	69	54	46	
17	1.84	59	890	136	11.6	55	60	40	2.2	54	60	40	,
		60	1010	151	9.2	60	60	40	2.2	26	83	17	
18	1.92	60	72	148	7.3	41	72	28	2.5	47	68	32	Nephrolithiasis + nephrectomia
		60	77	149	6.8	42	72	28	1.9	59	60	40	
		15	323	19	6.4	11	42	58	7.2	2	88	12	
19	1.64	15	373	19	5.3	12	37	63	8.0	1	95	5	Nephritis chron.
		15	260	19	5.3	14	26	74	7.2	0.4	98	2	
		30	435	16	5.3	9	44	56	7.1	2	88	12	
		32	410	16	5.0	9	44	56	7.9	3	82	18	
20	—	60	119	49	9.8	20	59	41	2.8	31	37	63	Nephrolithiasis
		60	137	52	8.4	24	54	46	4.1	18	65	35	
21	—	60	85	68	11.4	27	60	40	2.8	93	neg.	—	Hypertrophla prostatæ
		60	317	64	11.8	32	64	36	2.2	100	"	—	
22	—	60	115	17	7.0	8	53	47	5.0	32	neg.	—	Ostitis fibrosa generalisata.
		60	265	20	6.8	10	50	50	3.1	26	"	—	
23	—	67	134	65	8.0	25	62	48	2.5	29	55	45	Nephrolithiasis
		58	254	83	7.7	34	59	41	2.5	44	47	53	

Table 2.  
Sulfanil-amide.

Case No.	Body surface area m <sup>2</sup>	Period minutes	Urine ml	Inulin-clearance ml/min.	Free sulfanil-amide				Acetyl-sulfanil-amide				Diagnoses
					Plasma conc. mg/100 ml	Clearance	Apparently back-re-sorbed % of filtered	Apparently filterable part % of total	Plasma conc. mg/100 ml	Clearance	Apparently back-re-sorbed % of filtered	Apparently filterable part % of total	
24	—	60	248	112	4.4	51	55	45	5.0	46	59	41	Normal case
		60	290	110	4.4	43	62	38	4.1	43	62	38	
		60	188	105	4.0	45	57	43	3.6	53	50	50	
25	1.95	62	9	94	4.8	36	61	39	4.1	40	57	43	"
		60	325	86	4.8	35	59	41	3.6	46	47	53	
		60	385	83	4.4	40	52	48	3.6	53	37	63	
26	1.95	60	700	118	6.0	71	40	60	4.1	28	76	24	"
		59	180	139	5.6	53	62	38	3.6	33	74	26	
		61	360	168	5.6	56	68	32	3.6	33	80	20	
27	1.79	60	380	94	6.9	38	54	46	2.2	38	54	46	"
		60	502	108	6.9	38	65	35	2.3	50	46	54	
28	1.83	59	166	93	7.9	36	61	39	0.8	70	25	75	"
		60	310	121	6.4	45	63	37	1.0	35	71	39	
29	1.70	52	235	40	5.2	19	53	47	5.5	18	81	19	Hypertroph. prost.
		60	345	35	5.2	19	46	54	4.6	29	66	34	
		60	270	34	4.4	18	47	53	3.6	13	84	16	
30	1.83	60	490	81	5.3	42	48	52	2.5	18	78	22	Polyarthr. chron.
		60	330	70	5.0	38	46	54	2.5	25	65	35	
31	1.91	60	86	8	5.6	5	44	56	4.0	8	0	100	—
		60	59	8	5.8	4	51	49	5.4	5	34	66	

place in the kidneys to a not inconsiderable extent. We thus cannot altogether exclude the possibility of an acetylation of sulfanil-amides there. The matter is being investigated in this laboratory.

The average clearance values we have found (table 7) for the different preparations and their acetyl compounds are on the whole in agreement with previously known data concerning the rate at which they are excreted with the urine and disappear from the blood.



Table 4.  
Acetyl-sulfa-thiazole.

Case No.	Body surface area m <sup>2</sup>	Period minutes	Urine ml	Inulin-clearance ml/min.	Acetyl-sulfa-thiazole				Diagnoses
					Plasma conc. mg/100 ml	Clearance	Apparently back-resorbed % of filtered	Apparently filterable part % of total	
90	—	30	430	141	2.4	24	83	17	Normal case
		30	340	147	2.5	32	78	22	
		30	123	99	2.3	35	65	35	
89	1.70	30	85	102	2.0	21	79	21	Hypertonia
		30	62	81	2.0	42	48	52	
		60	158	117	2.0	42	64	36	
92	—	60	343	132	1.9	32	76	24	Nephropathia gravidarum

The clearance for all the compounds tested seemed to be completely independent of the magnitude of the diuresis, of resorption of water ( $\frac{C_u}{C_p}$  for inulin), and of the concentration in the plasma of the compound in question. No indication of «self-depression» was to be observed within the concentration limits used by us.

For sulfanil-amide, sulfa-pyridine and sulfa-thiazole, as well as for their acetyl compounds, it proved that the amount that was apparently resorbed in the tubuli bore a strikingly constant relation to the amount filtered in the glomeruli, or alternatively: that the concentration of the apparently filterable part in the plasma bore a strikingly constant relation to the total concentration in the plasma. Which of these two ways of expressing the matter is the more correct one will be discussed later in this paper. This constant relation emerges both from the low dispersion for the values of the apparently resorbed part of the filtered sulfa-compounds and for those of the apparently filterable part of their plasma concentration (tables 1, 2, 3, 5, 7) and from fig. 1—6.

Table 5.  
Sulfa-methyl-thio-diazole.

Case No.	Body surface area m <sup>2</sup>	Period minutes	Urine ml	Insulin-clearance ml/min.	Creatinine-clearance ml/min.	Sulfa-methyl-thio-diazole		Diagnoses
						Plasma conc. mg/100 ml	Clearance	
43	1.82	62	430	139	—	6.7	240	Normal case
		60	710	129	—	6.2	191	
44	1.84	60	375	130	113	7.6	102	"
		60	438	133	107	11.0	104	
45	1.59	28	326	72	133	18.6	93	"
		30	341	91	—	18.1	89	
		61	402	83	120	15.4	94	
46	—	54	325	161	232	10.5	324	"
		62	274	199	234	8.1	324	
47	1.80	61	250	162	110	6.7	192	"
		62	603	108	90	4.8	176	
48	—	56	260	87	125	3.8	203	"
		60	364	75	99	2.9	140	
49	—	20	314	107	—	11.0	135	"
		60	932	83	—	11.2	123	
50	—	52	177	166	218	6.0	190	"
		65	655	126	178	3.0	168	
51	—	60	380	115	—	13.5	145	"
		60	198	109	—	13.5	163	
52	—	58	475	119	196	8.0	133	"
		60	323	110	174	5.8	164	
53	—	62	228	100	—	5.8	127	"
		58	252	81	—	5.5	119	
54	—	56	728	125	200	10.5	124	"
		59	740	89	129	7.5	126	
55	—	58	765	129	165	4.3	132	"
		61	305	114	157	3.0	145	
56	—	58	610	98	164	9.0	135	"
		62	562	87	145	8.0	125	

Case No.	Body surface area m <sup>2</sup>	Period minutes	Urine ml	Inulin-clearance ml/min.	Creatinine-clearance ml/min.	Sulfa-methyl-thio-diazole		Diagnoses
						Plasma conc. mg/100 ml	Clearance	
57	1.62	55	792	118	187	—	178	Nephrolithiasis
		60	395	87	165	—	141	
58	1.58	58	212	105	187	6.7	205	Nephrolithiasis
		60	86	87	137	4.8	150	
59	—	56	50	109	116	8.1	121	Hypertrophia prostatæ
		58	90	105	144	8.1	125	
60	1.56	60	300	156	—	5.3	108	Nephropathia gravidarum
		60	372	150	—	3.8	95	
61	1.56	60	464	122	—	3.1	104	"
		67	540	130	—	2.9	104	
62	2.05	60	40	143	—	8.3	138	"
		60	36	173	—	5.0	142	
63	—	60	380	119	127	12.8	148	The urogenital
		60	310	95	127	8.1	171	
64	1.90	60	214	137	141	6.7	148	Nephritis chronica
		60	824	210	182	4.3	208	
65	—	60	254	89	105	20.0	130	Nephrolithiasis + pyelonephr. chron.
		60	336	72	99	12.3	112	
66	—	60	280	109	102	8.6	83	Hypertrophia prostatæ
		60	170	88	84	8.6	81	
67	—	65	130	92	101	7.1	145	Nephritis chron.
		45	308	112	84	4.3	168	
68	1.75	60	133	6	9	9.5	6	"
		60	151	7	10	9.5	8	
69	—	60	125	15	21	8.5	19	"
		60	140	17	35	14.5	17	
70	—	60	110	8	16	12.8	6	Degeneratio cystica ren.
		60	127	11	17	13.8	7	
71	1.81	60	330	38	—	15.7	34	"
		60	350	23	—	11.4	39	
72	1.75	60	98	19	27	9.5	25	Hypertrophia prostatæ
		60	110	18	29	10.5	23	

Case No.	Body surface area m <sup>2</sup>	Period minutes	Urine ml	Inulin-clearance ml/min.	Creatinine-clearance ml/min.	Sulfa-methyl-thio-diazole		Diagnoses
						Plasma conc. mg/100 ml	Clearance	
73	1.75	60	84	25	32	13.3	22	Hypertrophia prostatæ
		60	124	26	32	11.4	30	
74	—	59	368	62	—	13.8	66	Nephritis chron.
		60	300	71	—	10.9	69	
75	1.65	60	135	55	—	15.4	54	Hypertrophia prostatæ
		60	300	37	—	11.4	63	
76	1.65	60	300	50	—	15.2	58	"
		60	380	71	—	11.9	71	
77	1.39	60	380	68	—	14.3	58	Status post eclampsism
		60	288	62	—	11.0	65	
78	1.92	59	44	28	38	—	64	Nephritis chron.
		61	120	28	37	—	78	
79	—	29	106	41	83	—	39	Cystopyelonephritis chron.
		31	140	37	83	—	37	
80	1.32	29	48	38	41	14.3	112	Nephrolithiasis + pyelonephritis chron.
		60	113	38	36	15.7	120	
81	1.74	60	358	66	120	9.0	66	Nephritis chron.
		58	339	60	95	7.0	60	
82	—	59	115	60	93	18.0	45	Hypertrophia prostatæ
		61	200	46	98	14.0	42	
83	—	60	165	50	87	6.5	61	"
		60	169	52	84	6.0	61	
84	1.74	60	180	62	105	6.0	170	Nephropatia gravidarum
		60	240	84	122	3.0	148	
85	1.75	60	95	41	—	7.5	38	Hypertrophia prostatæ
		82	215	35	—	8.0	41	
86	1.59	60	296	53	—	10.0	53	Pyelonephritis
		60	420	49	—	8.5	50	
87	—	60	312	63	—	15.5	86	Hypertrophia prostatæ
		60	410	53	—	13.5	89	
88	—	60	378	59	—	12.5	57	Hydronephrosis
		60	126	44	—	14.0	45	

Table 6.  
Acetyl-sulfa-methyl-thio-diazole.

Case No.	Body surface area m <sup>2</sup>	Period minutes	Urine ml	Inulin-clearance ml/min.	Creatinine-clearance ml/min.	Acetyl-sulfa-methyl-thiodiazole				Diagnoses
						Plasma conc. mg/100 ml	Clearance	Apparently back-resorbed % of filtered	Apparently filtered part % of total	
96	1.92	55	140	115	183	—	33	71	29	Normal case
		65	430	94	184	—	50	47	53	
93	1.74	67	182	21	53	4.7	12	75	25	Hypertonia + nephritis chron.
		54	134	19	41	6.7	10	90	10	
94	1.70	60	685	134	143	3.3	24	82	18	The renis + nephrectomia sin.
		60	440	94	127	4.0	27	71	29	
95	1.82	30	196	105	140	4.7	11	90	10	Diabetes insipidus
		27	264	129	171	5.0	17	87	13	
		63	440	92	135	4.0	15	84	16	

From this it appears also that the relations  $\frac{\text{resorbed amount}}{\text{filtered amount}}$  and  $\frac{\text{filterable amount}}{\text{total amount}}$  were completely independent of clearance, diuresis, resorption of water and other substances and of the concentration of the sulfanil-amides in the blood and urine. Variations and irregularities in the excretion of these substances are thus entirely proportional to changes in the magnitude of their filtration only. The resorption in the tubuli seems always to be a constant function thereof, or alternatively: only a constant part of the substance dissolved in the plasma seems to be filterable.

The clearance values for these three sulfanil-amides are all considerably lower than those for inulin clearance. Several investigators who have observed their relatively low clearance have interpreted this as being due to a resorption in the tubuli of the substance in question, that would then have the same concentration in the glomerulus filtrate as in the plasma. There are, however, three possible explanations of the observation in question.



Table 7.

Average values of inulin-clearance, sulfa-clearance, apparent back-resorption in per cent of filtered and apparently filterable part in per cent of total plasma concentration in the normal cases and the correlation coefficient for  $\frac{Cu}{Cp}$  for inulin to  $\frac{Cu}{Cp}$  for sulfa compound in all cases, normal and pathological.

	Number of cases		Inulin-clearance		Sulfa-clearance		Apparent back-resorption in % of filtered		Apparently filterable in % of total		Number of cases		Correlation coefficient $\frac{Cu}{Cp}$ inulin to $\frac{Cu}{Cp}$ sulfa-compound
	average value	$\sigma$	average value	$\sigma$	average value	$\sigma$	average value	$\sigma$	average value	$\sigma$			
Free sulfa-thiazole	135.94 $\pm$ 3.96	15.82	54.5 $\pm$ 1.90	7.61	59.7 $\pm$ 1.49	5.95	40.3 $\pm$ 1.49	5.95	24	0.95 $\pm$ 0.02	17		
Acetyl-sulfa-thiazole			26.9 $\pm$ 4.21	17.33	80.6 $\pm$ 3.18	13.10	19.4 $\pm$ 3.18	13.10	23	0.55 $\pm$ 0.15			
Free sulfa-pyridine	131.75 $\pm$ 16.76	44.42	29.5 $\pm$ 3.42	9.03	75.0 $\pm$ 4.83	12.75	25.0 $\pm$ 4.83	12.75	11	0.76 $\pm$ 0.13	8		
Acetyl-sulfa-pyridine			40.1 $\pm$ 8.37	22.09	66.4 $\pm$ 8.12	21.44	33.6 $\pm$ 8.12	21.44	11	0.30 $\pm$ 0.30			
Free sulfanil-amide	109.1 $\pm$ 8.91	17.87	44.1 $\pm$ 4.20	8.40	58.8 $\pm$ 0.97	1.94	41.2 $\pm$ 0.97	1.94	8	0.95 $\pm$ 0.04	5		
Acetyl-sulfanil-amide			44.2 $\pm$ 3.60	7.25	55.8 $\pm$ 5.58	11.16	44.2 $\pm$ 5.58	11.16	8	0.81 $\pm$ 0.15			

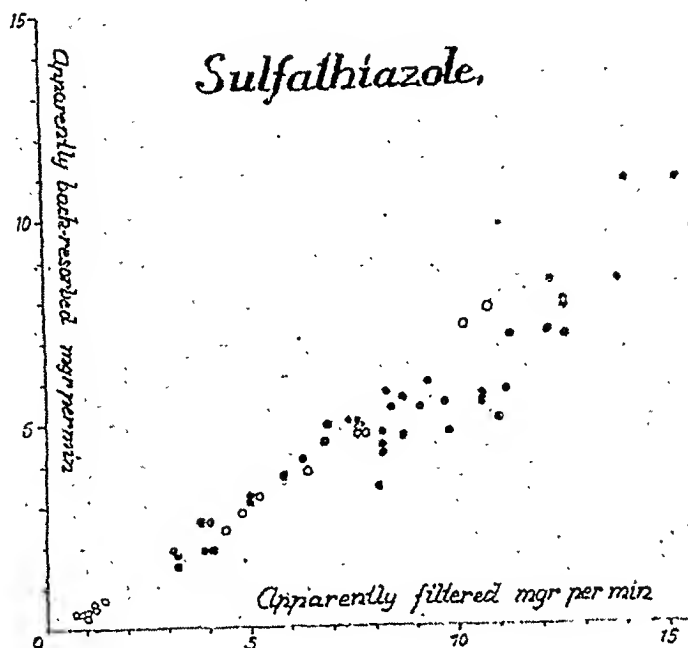


Fig. 1.

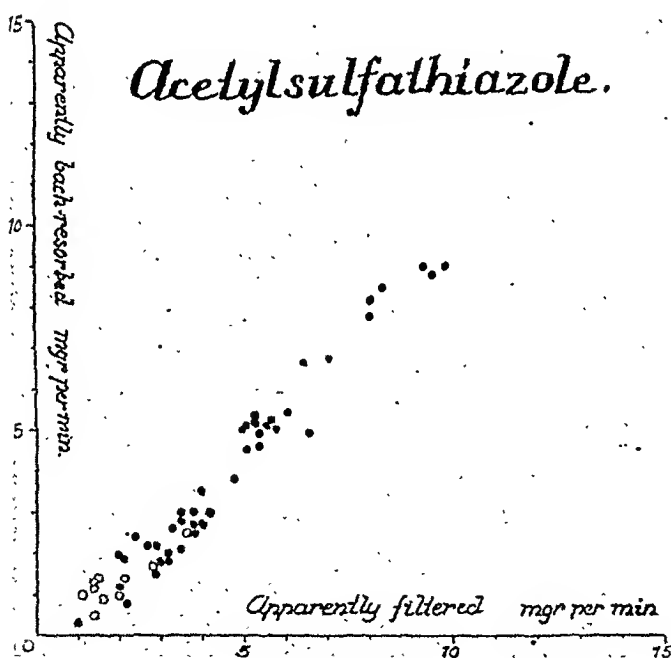


Fig. 2.

Fig. 1—6. Amount sulfa-compound apparently reabsorbed in the tubules (ordinate) as a variable to the amount apparently filtered in the glomeruli (abscisse). Each dot represents one clearance period. ● — cases with normal kidneys, ○ — cases with kidney diseases. The nearly linear correlation is to be observed, indicating either that a constant part of the filtered amount is reabsorbed or that a constant part of the amount in the blood is filtered.

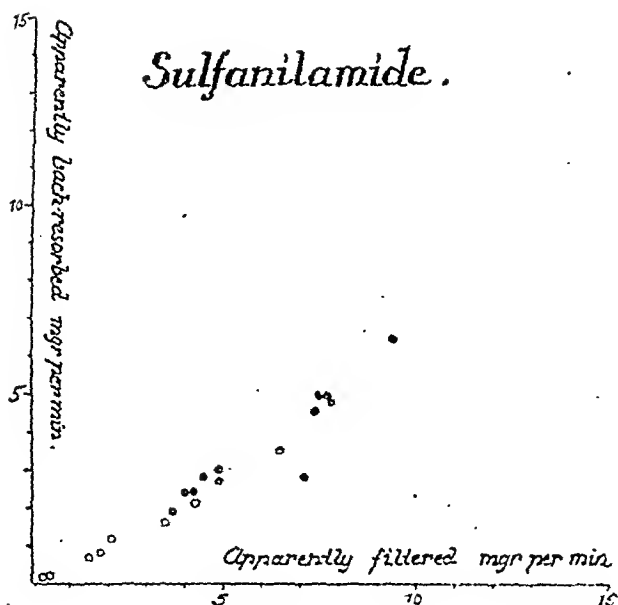


Fig. 3.

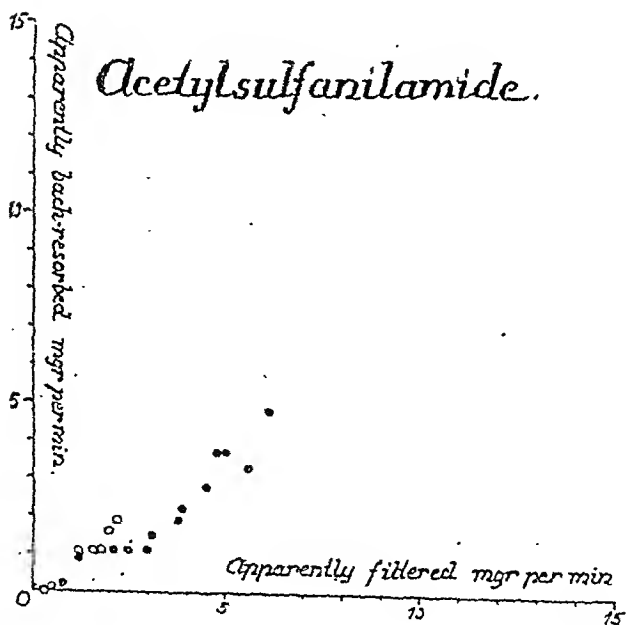


Fig. 4.

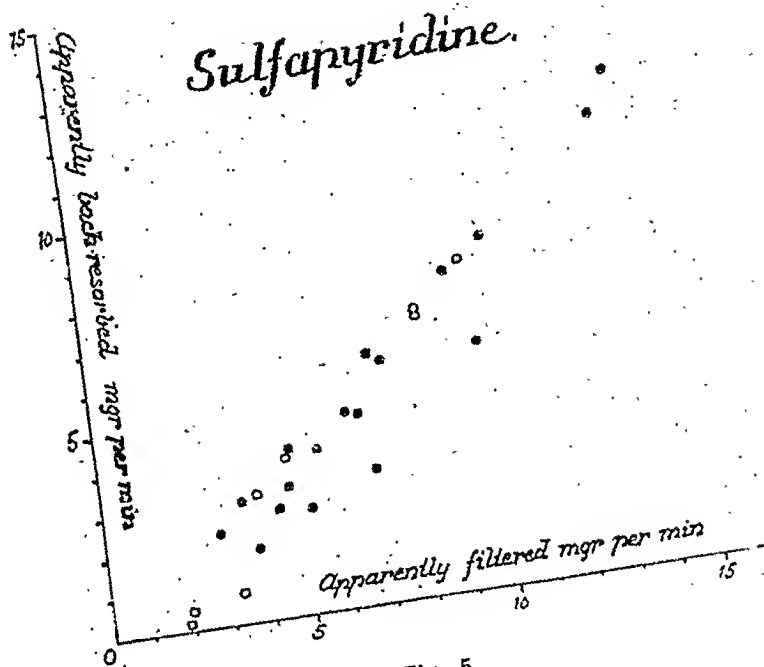


Fig. 5.

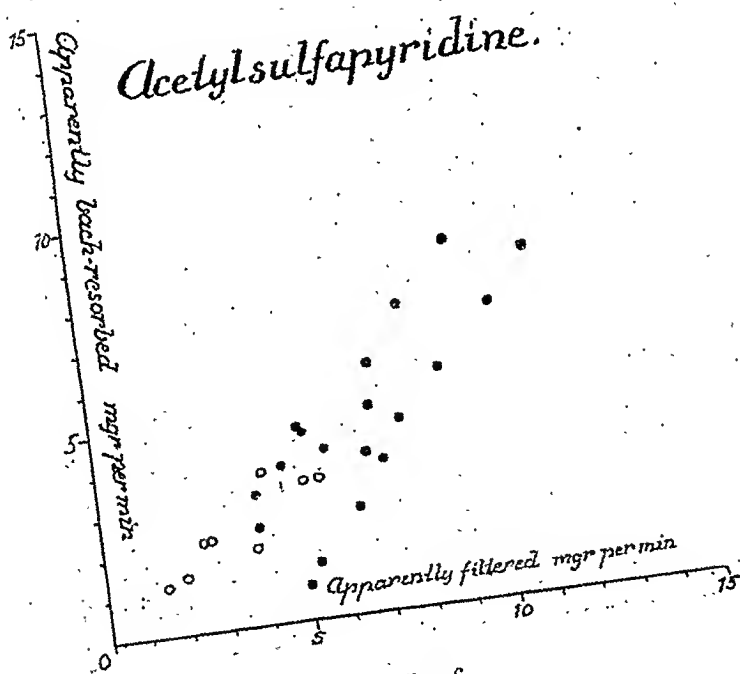


Fig. 6.

One of these possible explanations is that the sulfanil-amide derivatives pass through the cellular membranes in the glomeruli at a slower rate than water, inulin, creatinine etc. This explanation seems to us, however, rather improbable. The sulfanil-amides are comparatively small molecules and there does not seem to be any reason why they should pass the glomerular membranes slower than inulin with its large molecule size.

The second explanation is that a part of the sulfanil-amides occurring in the plasma might exist in a non-filterable form (e.g. bound to protein). They would nevertheless be quantitatively determinable as ordinary free sulfanil-amide by Marshall's method or a modification thereof. The other unbound part of the substances would then be freely filterable. Some recently published observations speak in favour of this explanation. Thus, in connection with the ultra-filtration of sulfa-thiazole-containing plasma, Andersen, Möller and Simesen (1942) found that only  $1/5$ — $1/3$  of the sulfa-thiazole was ultra-filterable; the rest remained behind with the proteins. It seems natural to assume that the part of the sulfa-thiazole that was not ultra-filterable was also not filterable in the glomeruli. They also found that acetyl-sulfa-thiazole in plasma was less ultra-filterable than the free compound, an observation that might well be combined with the circumstance noted by us that the acetyl-sulfa-thiazole has a lower clearance than the free sulfathiazole. In cataphoretic experiments Kimmig and Weselmann (1942) have found that certain sulfanil-amide derivatives migrate with the albumin in serum. Their analysis, however, were not quantitative, and the cataphoresis was carried out with a tension of 60 volts and without buffer-reserves at the electrodes. However, they found no migration at all in cataphoretic experiments with the sulfanil-amides in pure protein-free phosphate buffer solutions with varying hydrogen-ion concentrations. Further, in connection with attempts to ultra-filtrate serum containing a sulfanil-amide derivative through a filter impervious to protein, these writers found that only a part of the sulfanil-amide preparation was filterable, while the greater part remained behind in non-filterable form. At first glance these observations seem to lend support to the hypothesis that a considerable part of the sulfanil-amides dissolved in plasma exists in a form that is not filterable in the glomeruli. However, Kimmig's and Weselmann's observations indicating a

protein-binding were made on, *inter alia*, precisely sulfa-methyl-thiodiazole, i.e. the only sulfanil-amide preparation that seems to be filtered freely in the glomeruli, and in connection with which the hypothesis concerning the protein-binding is thus not compatible with the clearance values found. These experiments therefore seem to us to show that conclusions as to whether the sulfanil-amides are filterable in the glomeruli can scarcely be drawn from results obtained with ultra-filtration and cataphoresis.

Also worth mentioning in this connection is the fact observed by several investigators that the sulfa-thiazole-content in the blood is considerably higher than that in the cerebro-spinal fluid; the latter is protein-free, but approaches the concentration in the blood more and more closely the more protein-containing the c.s.-fluid is. (Andersen, Möller, Simesen 1942, Strauss, Lowell, Taylor, Finland 1941). On the other hand, it must be pointed out that this applies only to the sulfa-thiazole, but not to sulfanil-amide, that according to the same writers occurs in the blood and the cerebro-spinal fluid in about the same concentration; but the clearance of the sulfanil-amide is nevertheless lower than that of the sulfa-thiazole.

The third possible explanation of why the sulfanil-amides have a clearance that (with the exception of sulfa-methyl-thiodiazole) is so considerably lower than the inulin-clearance is the one that seems most obvious at the first glance and that appears to be the most generally accepted. It is that these substances are filtered freely with the water in the glomeruli and are then in part resorbed during the passage through the tubuli.

The first objection to this hypothesis is the above-mentioned circumstance that the amount resorbed in the tubuli — if the hypothesis were correct — has in our experiments proved to bear a very constant relation to the filtered amount of the same substance (figs. 1—6). This appears to be rather hard to reconcile with an active reabsorption where individual variations are to be expected. To a passive reabsorption there is the objection that we found the resorbed amount expressed as a percentage of the filtered amount to be completely independent of the water-resorption ( $\frac{C_u}{C_p}$  for inulin).

This independence can also be expressed in the following way: the relation between the urine concentration and the plasma

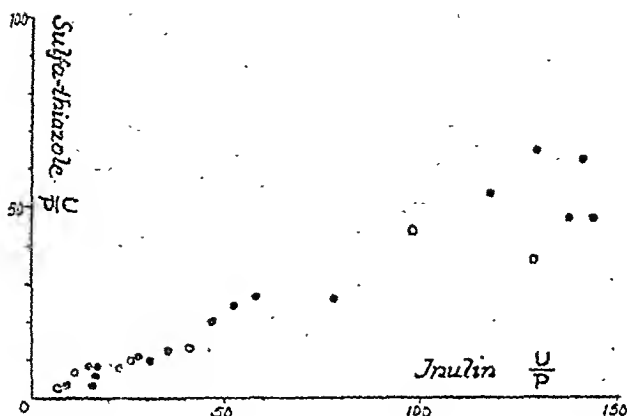


Fig. 7.

Fig. 7. Concentration index of sulfa-thiazole (ordinate) as a variable to that of inulin (abscisse). Each dot represents the average of one case. ● — cases with normal kidneys, ○ — cases with kidney diseases. The linear correlation indicates that the sulfa-compound is neither excreted nor reabsorbed during the passage through the tubules. The other sulfa-compounds gave similar results.

concentration  $\left(\frac{Cu}{Cp}\right)$  for the free sulfanil-amides has shown a clear, positive, nearly linear correlation to the corresponding relation for inulin in spite of widely varying diuresis (fig. 7).

That  $\frac{Cu}{Cp}$  for the sulfa-compounds must show a positive correlation to  $\frac{Cu}{Cp}$  for inulin is clear, as there is a positive correlation between filtered amount and amount reabsorbed in the tubuli of the sulfa compounds (see figs. 1—6). This can also be expressed in the following way:

$$\frac{\text{reabsorbed sulfa compound}}{\text{filtered sulfa compound}} = 1 - \frac{\frac{Cu}{Cp} \text{ sulfa}}{\frac{Cu}{Cp} \text{ inulin}}$$

For this reason we have demonstrated the relation

$$\frac{\frac{Cu}{Cp} \text{ sulfa}}{\frac{Cu}{Cp} \text{ inulin}} \text{ in one figure only (No 7) e.g. for the sulfa-thiazole}$$

as these graphic demonstrations will be rather similar to the figs. 1—6

This straight-lined relation may best be explained by the assumption that only a certain constant part of the sulfanil-amides dissolved in plasma is filterable, and that none of them is resorbed in the tubuli. The concentration of the urine during the passage would, of course, in this case have the same effect on the concentration gradient of the inulin in the urine as on the sulfanil-amide, and  $\frac{C_u}{C_p}$  would change in the same way for both sulfanil-amide and

inulin. The fig. 7 shows that this was the case. If a reabsorption of the sulfanil-amides, active or passive, had taken place, the reabsorbed amount would, in these cases, bear an almost constant relation to the filtered amount, which for reasons given above is unlikely. In the case of the acetylated sulfanil-amides the relation  $\frac{C_u}{C_p}$  to  $\frac{C_u}{C_p}$  for inulin showed the same tendency as for the free com-

pounds. Here, however, the dispersion was considerable, without doubt owing to the greater experimental errors in the determination of these substances. The correlation coefficients of the relation  $\frac{C_u}{C_p}$  for inulin and the sulfanil-amides are given in table 7.

On the other hand, however, in connection with clearance experiments on a number of animal species Gammeltoft and Kjerulf-Jensen (1943) have found that if the animals were given levulose or galactose, these substances were resorbed in the tubuli to an extent that bore a very constant relation to the filtered amount. In their experiments it was assumed that all the levulose or galactose occurring in the plasma was freely filterable.

The questions as to whether the sulfanil-amides in plasma and their acetyl derivatives are freely filterable in the glomeruli and whether they are resorbed in the tubuli can thus not be finally decided with the support of existing evidence. For reasons given above we consider it, however, most probable that they are only in part filterable, and that they are not reabsorbed in the tubuli. The thus filterable amount of each sulfanil-amide derivative seems to bear a very constant relation to the total amount of the same derivative in the plasma. This does not exclude the possibility that a certain part of the sulfanil-amides of the plasma, proportional to the concentration, is excreted by the tubular



cells. Further investigations in the matter are being carried on in this laboratory.

The forms in which the sulfanil-amides occur in plasma and the filterability of these forms are of interest not only with regard to the manner in which these substances are excreted in the kidneys, for it may also be possible to draw comparisons with the manner in which they penetrate into other organs and body fluids as well as into bacteria. It is thus worth noting that sulfathiazole only slowly makes its way into the cerebro-spinal fluid, and that the concentration there seldom exceeds four-fifths of that of the plasma, and is generally even considerably lower (Strauss, Lowell, Taylor, Finland 1941), while the unsubstituted sulfanil-amide enters rapidly and assumes the same concentration in the cerebro-spinal fluid as in plasma. It has been shown that these preparations diffuse in a similar way into cells, erythrocytes etc. Nonetheless sulfa-thiazole has on an average a higher clearance than the free sulfanil-amide. In this connection it is also deserving of note that the free sulfanil-amide derivatives seem to diffuse rather freely from the blood of the mother to that of the embryo (Lee, Anderson, Chen 1938, Kayser 1941, Speert 1943), while the acetyl derivatives, that have a relatively low clearance, enter slowly and in proportionally lower concentrations (Andersen, Simesen 1942).

## II. *Sulfa-methyl-thiodiazole.*

We have been able to confirm the curious circumstance discovered by Frisk in 1943, that sulfa-methyl-thiodiazole has a clearance that diverges radically from that of other tested sulfanil-amides, being of the same order of magnitude as the creatinine and inulin clearances. Earlier the rapid and complete excretion of this substance with the urine had been described by Andersen, Schmith and Søbye (1942) and by Vonkennel, Kimmig and Korth (1940). Frisk, who determined the clearance of this compound simultaneously with that of creatinine, found it in one case to be the same as the creatinine clearance and in seven cases to be somewhat lower.

In our material (table 5) we have in some of the cases with healthy kidneys arrived at similar results, but in some normal cases we have with this substance found clearance values even considerably exceeding that of the creatinine. In our cases with reduced clearance, on the other hand, the clearance of the sulfa-me-

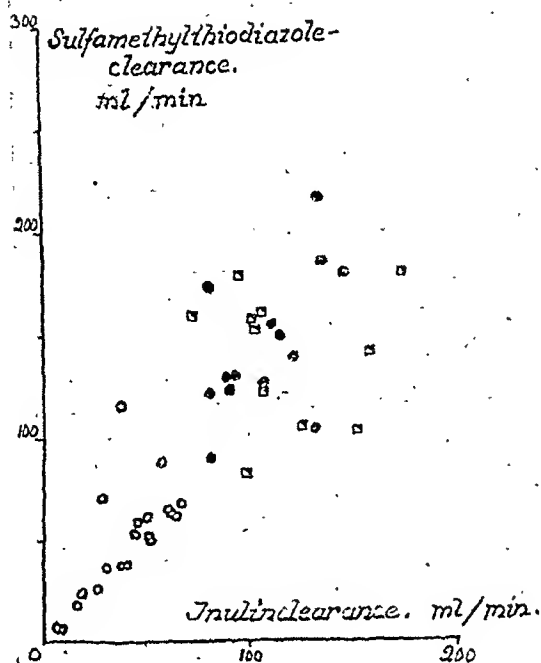


Fig. 8.

Fig. 8. Sulfa-methyl-thiodiazole-clearance (ordinate) as a variable of inulin-clearance (abscisse). Each dot represents clearance average of one case. ● — cases with normal kidneys and normal inulin-clearance. ■ — cases with signs of kidney diseases but with normal inulin-clearance, ○ — cases with kidney diseases and subnormal inulin-clearance. Note the good correlation between the two clearances in the pathological cases with low clearance.

thyl-thiodiazole was mostly lower than that of the creatinine, and showed herein good agreement with the inulin clearance (fig. 8).

This agreement was in point of fact so good that it shows that one might employ the sulfa-methyl-thiodiazole as a clearance substance for clinical use in testing the kidney function. From the clinical point of view, moreover, it is chiefly in cases with reduced clearance that an accurate determination of the glomerulus filtration is of interest, and in these cases the clearance of the sulfa-methyl-thiodiazole can, as we have seen, be regarded as agreeing well with the inulin clearance.

In our material only two of the cases with reduced clearance diverged to any extent worth mentioning from this rule (Nos. 78 and 80). In these two cases the clearance of the sulfa-methyl-thiodiazole was considerably higher than both that of the inulin and

that of the creatinine — an indication of a considerable tubular excretion of sulfa-methyl-thiodiazole. One of the cases was a nephrolithiasis with pyclo-nephritis, the other a chronic nephritis.

In those cases where the inulin clearance showed a fairly good or good glomerulus filtration (the lower limit being about 70 ml per min.) the agreement with the sulfa-methyl-thiodiazole clearance was poorer. In the majority of cases the latter clearance was considerably higher than that of the inulin, and in many cases also higher than that of the creatinine. However, even in these cases there was a fairly good correlation between the sulfa-methyl-thiodiazole and the inulin clearance in spite of the fact that the former one was higher than the latter.

The sulfa-methyl-thiodiazole clearance is also in many respects easier to determine, and gives fewer experimental errors than does the inulin clearance. As the preparation can be taken by mouth it is also simpler to administer than inulin, that must be given in voluminous injection. The determination of sulfa-methyl-thiodiazole in plasma can be carried out on so little as 0.1 ml. This amount of plasma can easily be obtained from the blood by pricking a finger-tip or the lobe of an ear, if one uses Josephson's (1943) plasma pipette. This is of special importance in clearance determinations on children.

Our results agreed with the assumption that both creatinine and sulfa-methyl-thiodiazole, like inulin, are freely filtered in the glomeruli, but that normally both sulfa-methyl-thiodiazole and creatinine are to some extent excreted in the tubuli, though the creatinine usually in a higher degree than the former.

It is a difficult matter to interpret the circumstance that the sulfa-methyl-thiodiazole clearance generally exceeds that of the inulin. A possible, though not very plausible, explanation would be that only the sulfa-methyl-thiodiazole clearance corresponds to the glomerular filtration, while inulin might in normal kidneys be slowly filtered, that would cause the glomerulus filtrate to have a lower concentration of inulin than the blood plasma.

But the most likely explanation is that the sulfamethyl-thiodiazole has in these cases also been excreted in the tubuli. It is worth noting that in cases where the glomerular filtration is reduced, as a rule also the tubular excretion of sulfamethyl-thiodiazole is reduced, as is the case with the tubular excretion

of creatinine. This reduction of the function in the tubular epithelium seems to be rather parallel with the glomerulus injury.

The circumstance that the sulfa-methyl-thiodiazole seems able to be excreted in the tubuli is of great interest. Frisk (1943) found that both sulfa-thiodiazole and sulfa-ethyl-thiodiazole have a much lower clearance than the corresponding methyl compound. It appears, moreover, from our tables that the acetylated sulfa-methyl-thiodiazole has a low clearance — about the same as that of the acetylated sulfa-thiozole. In these experiments (table 6) the subjects were given only acetylated, not free, sulfa-methyl-thiodiazole.

### III. *Clinical points of view.*

From the clinical point of view it may be worth observing that the sulfanil-amide excretion in the kidneys seems to be completely independent of the diuresis. By giving patients treated with these preparations plenty to drink one of course diminishes the risk of concrement formation in the kidneys. One does not, however, hasten their excretion as is often assumed, provided that the glomerulus filtration does not increase e.g. by diminution of the protein-concentration in the blood. The sulfanil-amide excretion seems in general not to be affected by any other means than their plasma concentration and those which increase or diminish the glomerulus filtration. According to Covian and Rehberg (1936), the filtration sinks during muscular exercise, so that one may expect that the sulfanil-amide derivatives will be excreted more slowly in patients who are continuing with their work than in those who are confined to bed. The risk that is generally assumed to exist of giving patients with kidney trouble sulfanil-amide preparations would appear to be rather slight, since the sulfanil-amide excretion in the glomeruli diminishes with a diminishing glomerular filtration and the filterable amount of the sulfanil-amide is constant in relation to the amount dissolved in plasma.

Fishberg (1942) found also in cases with kidney insufficiency a slow excretion of sulfanil-amides, slight risk of precipitation in the kidneys and a good effect on the infections amenable to therapy. This is not in agreement with Lindner's and Acheson's statement (1942) to the effect that the blood concentration had nothing to do

with the possible crystallization of sulfa-thiazole in the kidneys. The amount excreted per time-unit is, with a certain margin of error, directly proportional to the blood concentration, so that in cases of high blood concentration greater diuresis is needed than in cases of low concentration to prevent crystallization.

It is also of a certain interest to observe in what degree the clinical condition of the subject has proved to affect the excretion relations of the sulfanil-amides in the kidneys. In cases with kidney ailments, as already mentioned, it proved that the clearance of sulfa-methyl-thiodiazole, with but few exceptions, agreed strikingly well with the inulin clearance when the latter was below the normal value. In three cases of pregnancy with mild symptoms of kidney disease (nephropathy occasioned by pregnancy) but with normal inulin clearance, the sulfa-methyl-thiodiazole clearance was lower than the inulin clearance. In nearly all the other kidney cases that showed normal clearance the sulfa-methyl-thiodiazole clearance was higher than that of the inulin. This might be interpreted to mean that in these cases of pregnancy the tubuli but not the glomeruli were injured, so that the tubular excretion of sulfa-methyl-thiodiazole was reduced but not the glomerulus filtration. Unfortunately, the creatinine clearance was not determined in these cases; but investigations are being continued along these lines.

For the other tested free and acetylated sulfanil-amides it proved that the clearance both in cases with kidney affections and in those with reduced inulin clearance without other kidney symptoms was on the whole in proportion to the inulin clearance (fig. 8). When the latter was reduced it was found that with few exceptions also the sulfa-clearance was diminished below the usual value for healthy kidneys.

### Summary.

The renal clearances of some sulfanil-amide-derivatives have been determined in a number of human subjects with healthy kidneys and with kidney diseases or low inulin clearance.

The following substances were investigated:

- sulfanil-amide,
- sulfa-pyridine,
- sulfa-thiazole, and
- sulfa-methyl-thiodiazole.

Both the free and acetylated compounds were determined in blood-plasma and urine.

In all cases the inulin clearance (and in some cases the creatinine clearance) was determined simultaneously with the sulfa-clearance during at least two and often three consecutive periods. The clearance values found varied considerably for each preparation. The free substances showed clearances within the order of magnitude found by earlier investigators. The acetylated compounds, on the other hand, gave considerably lower clearance values than those earlier observed. This was most obvious in the case of acetyl-sulfa-thiazole. In the cases of acetyl-sulfa-thiazole and acetyl-sulfa-methyl-thiodiazole the clearance values found were confirmed by experiments on subjects who were given the acetyl compounds only.

The proportion between the different sulfa-clearances and the inulin clearance was rather constant within wide limits. Sulfa-methyl-thiodiazole had a clearance similar to or a little above that of inulin; but all the other preparations tested as well as their acetyl derivatives, including that of sulfa-methyl-thiodiazole, showed clearance values considerably below that of inulin.

The sulfa-clearance was as a rule diminished below the normal value together with the inulin clearance in cases of impaired kidney.

The cause of the difference between the sulfa-clearance and the inulin clearance has been discussed, and the following three possibilities considered:

1) a part of the sulfa-preparation may be bound in the plasma in such a way that it cannot be filtered in the glomeruli, while the remaining part is freely filterable;

2) the sulfa-preparations may filtrate completely into Bowman's capsule, but the filtration may be slower than that of water and inulin;

3) the sulfa-preparations may be completely and freely filterable but partly resorbed in the renal tubules.

It is not at present possible to determine definitely which of these possibilities constitutes the correct explanation of the difference between the clearances. We consider, however, that the first one is the likeliest. Of course, combinations of these three possibilities are also conceivable and an excretion into the tubuli can

not be excluded. The proportion between filterable sulfa-preparation in the plasma and the total concentration was determined for the free as well as for the acetylated compounds on the basis of the clearance values for the sulfa-preparations and for inulin. Alternatively, the magnitude of the hypothetical back-resorption in the tubules as a percentage of the filtered amount was calculated in the same way.

It was found that the proportion between filterable and total sulfa-preparations in the plasma was very constant. Alternatively, a very constant part of the amount filtered was reabsorbed in the tubules. This was true as well for the free as for the acetylated compounds. The proportion was quite independent of the magnitude of the clearance, diuresis, back-resorption of water, pathological condition of the kidney and the concentration of the sulfa-preparation in the plasma. The problems of the filtration, excretion and reabsorption of the sulfa-preparations are now being further investigated in this laboratory.

The clearance of sulfa-methyl-thiodiazole was of particular interest, as with but few exceptions it was found to be practically identical with the inulin clearance in cases with a decreased glomerular filtration. In cases with normal filtration the sulfa-methyl-thiodiazole clearance was usually higher than the inulin clearance, indicating a tubular excretion of the former substance. Determination of the sulfa-methyl-thiodiazole clearance is suggested as a routine clinical kidney function test.

In three cases of nephropathy incident to pregnancy with normal inulin clearance the sulfa-methyl-thiodiazole clearance was a little lower than that for inulin, indicating a tubular impairment.

As the clearance of the sulfanil-amides seemed to bear a rather constant proportion to the glomerular filtration (inulin clearance), and as neither their clearance nor the relation between the filterable and non-filterable amounts (alternatively: between the filtered and the reabsorbed compounds) can be influenced by changes in diuresis or water-reabsorption, their excretion through the kidneys cannot be influenced by increased intake of water or by thirst.

## Bibliography.

- Alving, A. and Miller, B.: A Practical Method for the Measurement of Glomerular Filtration Rate, *Arch. Intern. Med.* 66, 306, Aug. 1940. — Andersen, H., Möller, K. and Simesen, M.: Über die Zustandsform von Sulfathiazol im Blut, Urin und in der Cerebro-Spinalflüssigkeit. *Arch. exp. Path. u. Pharm.* 199, 528, March 1935. — Andersen, H. and Simesen, M.: Über den Übergang von Sulfathiazol, Sulfapyridin und Sulfamethylthiazol von der Mutter zum Fötus, *Arch. exp. Path. u. Pharm.* 199, 521, March 1942. — Andersen, T., Schmidth, K. and Søbye, P.: Eksperimentelle og kliniske Undersøgelser over 2-sulfanilamido-5-methyl-1, 3, 4 tiodiasols (Lucosils) Virkning paa Pneumocoeinfektioner. *Ugeskr. f. læger* 104, 2, 5, febr. 1942. — Bratton, C. and Marshall, E. K.: A New Coupling Component for Sulfanil-amide Determination, *Journ. Biol. Chem.* 128, 537, May 1939. — Coreoran, A. C. and Page, I.: Applications of Diphenylamine in the Determination of Levulose in Biological Media, *Journ. Biol. Chem.*, 127, 601, March 1939. — Covian, G. and Rehberg, B.: Über die Nierenfunktion während schwerer Muskelarbeit, *Skand. Arch. f. Physiol.*, 75, 21, Sept. 1936. — Ekelhorn, G.: *Acta Med. Scand.* 17, 114, 1944. — Fishberg, A.: The Use of Sulfonamides in Renal Insufficiency, *Journ. Mt. Sinai Hosp. N. Y.* 8, 509, 1942. — Frisk, R.: The Renal Clearance of Various Sulfanilamide Derivatives and the Distribution of Free and Conjugated Compounds between Corpuseles and Plasma in Man, *Acta Med. Scand.*, 106, 404, Jan. 1941. — Frisk, R.: Sulfanilamide Derivatives, *Supplem.* 142, 1, *Acta Med. Scand.* Febr. 1943. — Gammeltoft, A. and Kjerulf-Jensen, K.: The Mechanism of Renal Excretion of Fructose and Galactose in Rabbit, Cat, Dog and Man (with special reference to the phosphorylation theory), *Acta Physiol. Scand.*, 6, 568, Dec. 1943. — Hecht, G.: Ullron Bestimmungen in Körperflüssigkeiten, *Dermat. Wochenschr.*, 106, 261, Febr. 1938. — Josephson, B.: An Apparatus for Obtaining an Exact Amount of Plasma from a Small Quantity of Blood, *Acta Physiol. Scand.*, 6, 282, Nov. 1943. — Josephson, B. and Lindahl, O.: On the Reliability of the Inulin Clearance together with a Comparison between this and the Creatinine Clearance, *Acta Med. Scand.*, 116, 20, Dec. 1943. — Kayser, H. W.: Sulfonamidwirkung auf Mutter und Kind unter der Geburt, *Klin. Wochenschr.*, 20, 510, May 1941. — Kimmig, J. and Weselmann, H.: Die Bindungsverhältnisse zwischen Bluteiweisskörper und Sulfonamiden, *Arch. f. Dermatol. u. Syphilis*, 182, 436, Dec. 1942. — Lee, H. M., Anderson, R. L. and Chen, K. K.: Passage of Sulfanilamide from Mother to Fetus, *Proc. Soc. Exp. Biol. Med.* 38, 366, April 1938. — Lieb, H. and Zaackel, M. K.: Untersuchungen über den Kreatin- und Kreatininstoffwechsel, *Zeitschr. physiol. Chem.* 223, 169, Febr. 1934. — Lindner, H. and Acheson, D.: Sulfathiazole Crystallization in the Kidney, *Journ. Urol.*, 47, 262, Febr. 1942. — Marshall, E. K.: Determination of Sulfanilamide in Blood and Urine, *Journ. Biol. Chem.*, 122, 263, Dec. 1937. — Miller, B. and Winkler, A.: The Renal Excretion of Endogenous Creatinine.



and Inulin, Journ. Clin. Invest. 17, 31 June 1938. — Reinhold, J., Flippiu, H., Schwartz, L. and Domm, A.: The Absorption, Distribution and Excretion of 2-Sulfanilamido pyrimidine (Sulfapyrimidine, Sulfadiazine) in Man, Amer. Journ. Med. Sci., 201, 106, Jan. 1941. — Shannon, J.: The Renal Excretion of Creatinine in Man, Journ. Clin. Invest., 14, 403, July 1935. — Smith, Homer: The Physiology of the Kidney, Oxford University Press, 1937. — Speert, H.: Placental Transmission of Sulfathiazole and Sulfadiazine and its Significance for Fetal Chemotherapy, Amer. Journ. Obstetr. Gynecol., 45, 200 Febr. 1943. — Strauss, E., Lowell, F., Taylor, L. and Finland, U.: Observations on the Absorption, Excretion and Distribution of Sulfanilamide, Sulfapyridine, Sulfathiazole and Sulfamethylthiazole, Ann. Intern. Med. 14<sup>II</sup>, 1360, Febr. 1941. — Svartz, N.: Salazopyrin, a New Sulfanilamide Preparation, Acta Med. Scand., 110, 577, July 1942. — Taylor, L., Lowell, F., Adams, M., Spring, W. and Finland, M.: A Comparative Study of the Blood Concentrations and Urinary Excretion of Sulfapyridine and Sulfanilamide after Single Doses of Sulfapyridine and Related Compounds Administered by various Routes, Journ. Clin. Invest., 19, 201, Jan. 1940. — Vonkennel, J., Kimmig, J. and Koth, B.: Versuche und Untersuchungen mit neuen Sulfonamiden, Zeitschr. f. klin. Med., 138, 695, Dec. 1940.

---

### III.

## The normal excretion of urinary constituents of low tubular reabsorbability together with remarks concerning the variability of glomerular filtration.

By

GÖSTA EKEHORN.

Stockholm.

(Submitted for publication August 28, 1944).

---

The relations between the degree of tubular resorbability of a given urinary constituent, its Renal Extraction Rate, and its general level in the plasma.

In a preceding paper in this Journal (Ekehorn, The importance of adequately recorded results in renal tests. Acta med. Scand., 1944, 119 p. 57) I called attention to several points of difference regarding the renal excretion of water and other threshold-substances of the urine, on the one hand, and of some important urinary waste-products, on the other. I mentioned that these differences all derived from the fact, that the waste-products were much less resorbable in the renal tubules than the threshold-bodies: thus no creatinine and only up to some 50--60 % of the urea are normally reabsorbed after filtration in the glomeruli, whereas only more or less minute fractions of filtered water and chlorine escape tubular reabsorption and pass over into the final urine.

This low tubular resorbability of the waste-products makes their *Renal Extraction Rates* much higher than those of water and solid threshold-bodies (loc. cit. 57); we recollect, that the R.E.R. of urinary constituents is defined as their excreted quanti-

ties expressed as a percentage of the total quantities contained in the blood, that passes through the kidney during the period of their excretion (this journal. vol. 118, p. 143—45).

Thus, the R.E.R. of water is usually only about 1 ‰; even in most excessive water diuresis it rises only to 2—3 %; the R.E.R. of chlorine is of about the same low order of magnitude. The R. E. R. of the waste-products is very much higher; thus it amounts with creatinine to some 16—22 % in normal rabbits (Ekehorn, Inulin as a substitute for creatinine in renal tests, this journal vol. 118 p. 146; Über die Bedeutung der renalen Anschwemmungsgrade, Virchows Arch., 1935, 295, p. 260—61, 269—71.); it is the same or perhaps somewhat higher in healthy human kidneys (Ekehorn, Principles of renal physiology, p. 601—619—630; Integrative Natur der normalen Harnbildung, p. 245—48; 315—18. Ekehorn, Virchows Arch., 1932, vol. 284, p. 375—82; *ibid.* vol. 285, p. 615—21). The R.E.R. of urea 5—8 % in normal rabbits and may rise to 13 %; it is normally about half the R.E.R. of creatinine in man, *i.e.* about 10 %, and may rise to over 15 % under certain conditions.

These high R.E.R. of the waste-products have obviously also the effect of securing low levels of these substances in the blood. That is to say, because of these high R.E.R. their renal excretion becomes already at low plasma concentrations large enough to balance the metabolic production of these substances. This may be strikingly exemplified by a reference to creatinine.

Normally, the two human kidneys receive in 24 hours together at least 800, probably some 1200, and possibly some 1500 litres of blood (Ekehorn, Principles of renal Physiology, p. 586—598; Integrative Natur der normalen Harnbildung, p. 46—48.); this blood normally contains between 0.5 and 2 mg. creatinine per 100 cm<sup>3</sup>, which renders the 24-hourly supply of creatinine to the kidneys equal to (4—) 6—24 (—30) g. With a R.E.R. of 20 % for creatinine some (0.8—) 1.2—4.8 (—6) g creatinine are excreted with the urine; this is quite enough to balance the daily metabolic creatinine-production, which on a diet without meat is put at a little below 2 g per 24 hours. (Folin, Amer. J. Physiol. vol. 13).

Similarly, the R.E.R. normally being some 10 % in the case of urea in man, some 16—30 g urea will be excreted into the urine out of the 160—300 g that the blood in 24 hours conveys to the kidneys at a blood-urea level of 20 mg per 100 cm<sup>3</sup>. The 24-hourly urea production being some 20—25 g on a diet not too rich in nitrogen, the high R.E.R. renders it possible, at a plasma urea level of about 20 mg per 100 cm<sup>3</sup>, for renal urea excretion to balance urea production. If urea R.E.R. were only 5 % in the human kidney, similar quantities could be excreted first when plasma urea had risen to about 40/mg 100 cm<sup>3</sup>, and plasma urea would have to rise to some 200 mg/100 cm<sup>3</sup>, if the normal R.E.R. for urea only amounted to an average of 1 % etc.

The low tubular resorbability of the waste-products and their high Renal Extraction Rates are obviously closely connected with their removal from the blood in amounts sufficient for keeping their plasma concentrations low, *i.e.* in amounts that normally suffice both for balancing the metabolic formation of waste-products as well as for preventing their plasma concentrations from rising much above, what may still more or less be described as »only a trace».

Similar extensive removal from the blood is obviously quite out of question in the case of water and solid threshold-bodies, the tubular resorbability of which is very high and whose R.E.R.s are correspondingly very low.

These differences are connected with the fact, that the organism has no special interest in retaining *the waste-products* in the blood; on the contrary, it is to advantage the quicker they are excreted and the lower their plasma levels are maintained; nor does it matter much, exactly how low are their plasma levels, provided that they remain more or less low, and provided that temporary rises are brought down again reasonably quickly. In the case of *water and solid threshold-bodies*, on the other hand, the organism does not aim at all at removing them from the blood so completely that only mere traces are left. On the contrary, the organism aims at retaining them in the blood at constant levels, *i.e. on the one hand* the organism aims at reducing their excretion drastically, or quite stopping it if possible, whenever their plasma quantities fall below certain critical threshold-levels; *on the other hand* the organism must be able to augment their excretion by leaps and bounds whenever their plasma levels rise above their thresholds.

• This is not the place to describe in detail precisely how the kidney regulates the excretion of water and other threshold-bodies in realization of the above conditions; we recollect, however, the following points from my 2nd paper in *Acta med. Scand.* (vol. 119 p. 57).

1. The excreted quantities of *water and other threshold-bodies* are normally (*i.e.* in the healthy kidney where filtrate volume is abundant) practically quite independent of the absolute amounts filtered or reabsorbed.

2. The excreted quantities depend instead on the relative relations of filtered and reabsorbed amounts; *i.e.* on how much the reabsorbed amount of say, water, or chlorine, differs from the filtered water- or chlorine-amounts.

3. Reasons were given for crediting the renal tubules with at least a major, if not exclusive, rôle in the task of regulating these differences between the filtered and the reabsorbed amounts of the various threshold-bodies; it was also emphasized, that the filtrative-reabsorptive differences were regulated in strict accordance with the excretory exigencies of the respective threshold-bodies; attention was also drawn to the fact that this manner of regulating threshold-body excretion resulted in changes in the volume and composition of the urine with a powerful corrective influence on all deviations of these substances from their normal plasma thresholds.

4. The above and several other particulars are all due to the high tubular resorbability of *water and the other threshold-bodies*. Only more or less minute fractions of their filtered quantities escape subsequent reabsorption in the tubules; their amounts in the final urine represent in other words the small differences between the excessive quantities filtered and the almost as large quantities reabsorbed. It is evident from my 2:nd paper in this journal, that the above points and especially the high importance of the tubules for regulating the threshold-body output are rather axiomatic consequences of this.

5. In the case of *the waste-products*, on the other hand, emphasis must be laid on the fact that their low tubular resorbability makes them differ rather markedly from water and other threshold-bodies, more particularly with respect to how their excretion is regulated. The less a urinary constituent is affected by tubular activity, the less can also its excretion and its regulation be influenced by the tubules; it is therefore quite obvious, that great differences must also exist in this respect between the waste-products and the highly reabsorbable threshold-bodies.

\*

\*

\*

### The Excretion of Creatinine.

*Creatinine is filtered in the glomeruli and normally neither secreted nor reabsorbed by the tubules.*

The interest taken in the excretion of creatinine is chiefly due to its importance in Rehberg's test (cf. this journal vol. 118 p. 114). Several particulars regarding creatinine-excretion were discussed in some detail in my »Integrative Natur der normalen Harnbildung» (p. 85--89--105--109); as a matter of fact, the theoretical basis of the creatinine-test had been somewhat incompletely established in Rehberg's original paper. It is thus evident from the quoted pages, that Rehberg was unable to submit any entirely conclusive argument showing *that creatinine is filtered in the glomeruli and that the glomerular fluid is an ultrafiltrate from the plasma*; Rehberg's own observations and the observations contained in the contemporary literature sufficed only to indicate this mode of glomerular excretion as very probable; however, one or several links were missing in every chain of argument submitted. What I have styled »the protein proof of glomerular filtration» fills this gap and affords conclusive proof, that glomerular fluid is an ultrafiltrate from plasma (Integrative Natur etc. p. 30--31 and 89; Principles, p. 348--472--476; Virchows Arch. vol. 285, p. 455--460).

The other cardinal point in Rehberg's work is the idea, that *the tubules neither by secretion augment, nor by reabsorption diminish the filtered quantity of the creatinine*, i.e. that this quantity equals the creatinine in the final urine; the importance of this point is obvious from the introductory remarks and formulas of my first paper in this journal (vol. 118 p. 114). Rehberg's line of argument was, no doubt, highly suggestive, but was not conclusive.

His main argument was based on the fact that creatinine excretion is remarkably constant as long as the plasma-creatinine has the same level, and that creatinine-excretion is not influenced even by excessive changes of the volume or concentration of the urine or of the excreted absolute or relative amounts of the urinary solids (urea, NaCl, etc). According to all theories of tubular secretion as well as according to all theories of tubular reabsorption, the tubules must alter their activity when such changes occur; the independence of creatinine-excretion of these changes renders it highly

probable that it really is independent of tubular activities, as Rehberg thinks (Integr. Natur. p. 85—88). It is true, that creatinine differs rather markedly from all other normal and from most pathological urinary constituents in these respects; this difference, however, is less obvious as regards a number of artificially introduced plasma- or body-foreign substances, several of which may approach so closely to creatinine in these respects, that some further discussion becomes indicated, as to whether creatinine or some of these other substances really is the most suitable test-substance in Rehbergian tests, i.e. which substance is normally most independent of tubular activities.

The suitability of creatinine has been most energetically attacked by a school of authors, whose arguments have been scrutinized in my two preceding papers (this journal, vol. 118 p. 114 and vol. 119 p. 57); a very great number of observations made or alleged to have been made by these authors have been marshalled against creatinine as a test-substance, and renal physiology has for several years past been flooded by a real deluge of anti-creatinine arguments. Creatinine comes out triumphantly from this ordeal, however, as is very obvious from my earlier papers; indeed, every chain of arguments, alleged to demonstrate the unsuitability of creatinine and the superiority of another substance (inulin) was found to be altogether fallacious; it is superfluous to repeat here any of my earlier remarks against the substance of these anti-creatinine arguments, or against the often exceedingly surprising methods by which they were construed and presented to the reader.

Apart from the signal breakdown of this determined attack on Rehberg's ideas and ingenious work, his views regarding the *exclusively glomerular excretion of creatinine* receive a remarkable support from several later facts and observations.

Thus, I emphasized in my first paper in this journal (vol. 118, p. 131) the importance of Poulsson's paper (J. Physiol., 1930, vol. 69, p. 411), which the Inulin-propagandists contrived to pass over in such a surprising manner; his paper was also extensively discussed both in my »Principles (p. 677—78) as well as in my »Integrative Natur etc.» (p. 102—05). The well-established fact, that glucose is filtered in the glomeruli and normally completely reabsorbed by the tubules, precludes, of course, every possibility of the tubules

secreting it (cf. this journal, vol. 118 p. 131). Sufficient phloridzination completely paralyses this tubular glucose-reabsorption, i.e. glucose is under phloridzin changed into a substance that is neither secreted nor reabsorbed by the tubules, *and the glucose in the urine must therefore equal the filtered glucose*; that is to say, the clearance of glucose must, under complete phloridzin-paralysis of glucose-reabsorption, equal the volume of the glomerular filtrate according to the formulas given on p. 115—16 of my paper in vol. 118 of this journal. The fact, that this temporary clearance of the glucose approaches and even becomes equal to creatinine clearance, implies also, according to the same formulas, that creatinine is neither secreted nor reabsorbed by the tubules: the fact, that creatinine clearance remained of quite the same order in Poulsson's experiments prior to and under the phloridzination, indicates that the tubules do not secrete or reabsorb any creatinine whether they are phloridzinized or normal.

Poulsson's famous experiments have been universally recognized as exceedingly strong arguments in support of Rehberg's views, and this support is further strengthened by other Poulsson's experiments with certain sulphates in the unphloridzinized kidney (Z. ges. exp. Med., 1930, 72, p. 232). As pointed out for instance on p. 131 of my earlier paper, Poulsson's experiments come so near to conclusiveness that it really requires considerable critical acumen to see, that different modes of interpretation, although rather far fetched, are not quite precluded.

The validity and the theoretical importance of Poulsson's experiments, moreover, has been considerably enhanced during the last years. It is a curious fact, that this is due chiefly to observations made by the inulin-propagandists themselves. Indeed, these authors have shown that a great number of plasma- or body-foreign carbohydrates are subjected to some degree of tubular reabsorption after having been filtered in the glomeruli: they maintain energetically that these carbohydrates are reabsorbed as an admixture to glucose and by the tubular mechanism absorbing the latter, and they have in some noteworthy experiments also delivered decisive proofs that this is the case.

This resorptive mechanism may be prevented from reabsorbing artificially introduced body-foreign carbohydrates simply by injecting excessive quantities of glucose into the blood; the glucose-reabsorbing mecha-



nism becomes then so saturated with glucose that it fails to reabsorb all the filtered glucose as normally; it has then neither time nor space nor the power to reabsorb also the filtered foreign sugar. There can obviously be no question of tubular secretion of an otherwise tubularly reabsorbable sugar; cessation of its reabsorption will thus necessarily mean, that this sugar is neither secreted nor reabsorbed; its clearance must equal glomerular filtrate volume, and must also equal creatinine clearance if creatinine is likewise neither secreted nor reabsorbed by the tubules (cf. above, and the formulas there referred to). This has been shown to be the case with xylose in dogs, and is, of course, a very strong argument in favour of Rehberg's view. (cf. my paper in this journal vol. 118, p. 125—29).

Xylose and a number of other body-foreign sugars, all of them to some degree reabsorbable in the tubules, as the inulin-authors themselves maintain, have further been examined in phloridzinized kidneys, and under phloridzin they invariably obtain the same clearance as creatinine; *i.e.* the results conform entirely to Poulsson's similar phloridzin experiments with glucose, and must be interpreted accordingly as strong supports of Rehberg's views. Indeed, inulin itself, which is a polysaccharide, behaves just as the other carbohydrates under phloridzin and gets a clearance equal to that of creatinine even in those animal species where the two clearances differ in unphloridzinized kidneys.

It is true that the Inulin-protagonists interpret these experiments differently and try to persuade their readers that their results disagree with Rehberg's ideas. This is a direct misrepresentation of facts, however, (cf. my first paper. this journal vol. 118, p. 130—32—38).

Apart from all the above, Rehberg's views as regards the excretion of creatinine also receive remarkable confirmation from detailed analyses of tables of renal data, compiled according to his creatinine-method. It is already obvious from my second paper in this journal that a very preliminary analysis of such tables suffices to elucidate several matters of essential importance for the study of renal problems; the conclusions arrived at were also exceedingly obvious; indeed, they appeared more or less axiomatic as soon as due regard was taken of some very simple mathematical conceptions. It is also evident from my monograph »Integrative Natur» that properly studied Rehbergian tables are one of our principal means of carrying the analysis of renal functions sufficiently far, so as to extend the confines of renal physiology considerably and in several directions; it is also possible in this way to penetrate numerous and remote details, and to demonstrate the great physiological importance of several factors and circumstances, that earlier have been neglected to a consider-



the dissenting arguments and observations testifies strongly to the essential soundness of Rehberg's work. This soundness is rendered still more obvious by my immediately preceding remarks concerning a method that reveals earlier unknown but very important matters of clearly demonstrable reality etc.

\* \*

\*

*Further analysis of the excretion of creatinine.*

Rehberg's view, that urinary creatinine normally equals filtered creatinine, constitutes not only the theoretical basis of the creatinine test, but affords also *an explanation of the principal particulars characteristic of normal creatinine excretion*. Although Rehberg did not analyze his experimental results or follow up the implications of his conceptions very far, it is nevertheless very obvious that *creatinine excretion normally is approximately proportional to the plasma's concentration of the substance*.

The filtered creatinine-amounts are the products of this concentration and of the volumes of the glomerular filtrate. This implies, as I remarked in my second paper (this journal, vol. 119, p. 57), that the excretion of creatinine would be *quite proportional* to its plasma concentration, if the volume of the filtrate remained constant, but that the actually occurring fluctuations of this volume cause the filtered, and hence also the excreted creatinine quantities to deviate from a strict proportion to the plasma creatinine. I said also, that such deviations might occasionally be rather considerable; this was also rather evident from some of the curves illustrating creatinine-excretion in a number of experiments (loc. cit. p. 80, fig. 8). However, the filtrate-volume's positive and negative deviations from the mean volume largely balance each other; the consequent positive and negative fluctuations of filtered and excreted creatinine must therefore also largely balance each other. The more the periods of observation are prolonged, the less is, of course, the chance of filtrate-volume variations not being counterbalanced by opposite volume-fluctuations, and the less will occasional filtrate-volume fluctuations cause creatinine excretion to deviate from proportionality to the plasma creatinine. These

matters have been discussed in more detail elsewhere (cf. Integrative Natur etc. p. 206—07; p. 219); some emphasis was there laid on the fact, that the creatinine excreted in 6 hours, and still more the creatinine excreted in 24 hours, especially in the same individual, was fairly proportional to plasma creatinine, not withstanding the occurrence of not inconsiderable, and occasionally even large, deviations during short observational periods of 1—2 hours or less.

Both the occurrence of short-term deviations from the said proportionality as well as the gradual and mutual equalization of the positive and negative deviations is well apparent from figure 8 in my former paper. The figure refers to repeated observations during experiments lasting 4—5 hours, and, whatever short-term deviations may occur, there is no question but that mean creatinine excretion is at least roughly, and in some instances even rather closely, proportional, or parallel, to the level of the plasma creatinine — which in this instance is almost the same thing.

\*       \*

\*

### The variability of glomerular filtration according to the creatinine- and to the inulin-methods.

It has been alleged, that the creatinine-method gives an exaggerated idea of the fluctuations of the filtrate-volume, whereas less varying volumes would be obtained by the inulin-method. This alleged difference has then been marshalled as an argument indicating greater reliability of the inulin-method: inulin-clearance would be a truer measure than creatinine-clearance of the volume of the glomerular filtrate, because one obtains more constant figures for the former, the results of repeated determinations agree more closely and corroborate each other better than in the case of creatinine-clearance, etc.

These assertions have not been included in my earlier criticism of the alleged superiority of the inulin- over the creatinine-method (cf. this journal, my 1:st & 2:nd papers). I fear, that these assertions must be contested *both because* inulin-clearance is just as variable as creatinine-clearance *as well as because* everything points to the conclusion that lability, not constancy, is characteristic of glomerular filtration.

The question of the alleged differences between the two clearances appears never to have been particularly examined in the inulin-papers; the said assertion appears to be based only on a kind of general impression, that greater differences occur more frequently among the creatinine-clearance hitherto published in renal papers, than among the inulin-clearances.

It is obviously worse than useless to base very specific assertions on general impressions from a great mass of inulin- and creatinine-tests,

that have been performed by numerous workers in many countries, who with varying degrees of care and skill have examined the excretion of the most diverse urines under often vastly different physiological and experimental conditions. Assertions and conclusions with such questionable basis are especially uncertain in questions concerning the volume of the glomerular filtrate, because it can be clearly shown, also by means of the inulin-method, that *this volume may be much influenced by the experimental procedure.*

Thus, when Korr (Korr's paper has been discussed earlier in some detail in my 2:nd paper in *Acta med. Scand.* and in *Svenska Läkartidningen*, 1944, :24.) determined the filtrate volume in chickens by means of Smith's inulin-method, increases of the filtrate volume to about the double, and decreases to as little as 50 % of the usual volume, were, to judge from Korr's text, observed in all or practically all his experiments. Similar and even larger fluctuations are also depicted in all those diagrams, where Korr denotes filtrate-volume. Thus, in Korr's diagram nr 2 the filtrate volume fluctuates during 160 minutes between 4, 1.5, 8, and 6 cm<sup>3</sup> per minute in one and the same chicken; that is, the lowest and the highest inulin clearances relate here as 1: 5. These filtrate fluctuations are enormous relatively to the usual level of glomerular filtration in these small animals; their relative order surpasses considerably the widest variations ever to have been observed in creatinine-experiments on healthy human kidneys, not to mention the creatinine-variations usually met with.

This extraordinary instability of glomerular filtration in Korr's inulin-experiments is clearly due to the drastic nature of Korr's experimental procedure. »Unanaesthetized» chickens »were strapped, with outspread wings, with their backs to a specially designed board which held them in an almost vertical position.» »Unless otherwise stated the birds were fasted for 18 to 24 hours before observation» and many of them had been allowed no water for 48 hours. »Urine was collected through a glass tube 8—9 mm outside diameter, which fitted tightly into the cloaca» and the end of which pressed against the ureteral apertures. Several bloodsamples were drawn by puncture from a wing vein, whereas solutions of inulin, or inulin and urea, were continuously infused into another wing vein. The birds were given various injections (adrenine), and water through stomach tubes, etc. etc. Considering that the birds were unanaesthetized, and that chickens are silly and most easily frightened animals, the above list of experimental measures must be regarded as singularly provocative of haemodynamic changes and fluctuations of every kind; glomerular filtration is a haemodynamic process, the component factors of which are as numerous as labil (cf. below).

The above experiments make it very evident, that *regard must be paid to the experimental and physiological conditions*, if one desires



*other* is also borne out by the fact, that the ratio between the simultaneous clearances remains practically the same whatever the absolute order of the clearances. If we work out the *creatinine to inulin clearance ratio* in the above 7 determinations, we find the figures 1.25, 1.23, 1.21, 1.32, 1.22, 1.27 and 1.24, the mean of which is 1.25. A ratio, that varies only with a few units in the second decimal is, of course, to be regarded as practically constant, and these small variations of the ratio, moreover, are in all probability due to the circumstance that inulin is a less precise gauge of the volume of the glomerular filtrate than creatinine, as has been discussed in my paper in vol. 118 of this journal.

Josephson and Lindahl (Bertil Josephson and Olov Lindahl: On the reliability of the inulin-clearance together with a comparison between this and the creatinine clearance. *Acta med. Scand.* 1943, vol. 116, fasc. I, p. 20—32.) have also examined the inulin- and creatinine-clearances simultaneously in a series of patients. »50 patients with all kinds of diseases of the urinary system» were used in this series; the patients were of both sexes and of all ages from 18 years upwards. »About one hour before the determination was started they were given 3 g of creatinine by mouth according to Rehberg, and 10 g of inulin in a single injection of a 10 % solution.» »In all the patients the clearances were determined during two consecutive periods of about 60 minutes each.»

There is no question of creatinine clearance varying more than the inulin-clearance in all these pairs of simultaneous determinations, indeed, *creatinine clearance varies somewhat less*, although the difference is so small that it may well be due to chance or to experimental errors. As a matter of fact, »the standard deviation of the single determination» in these 50 cases was for *inulin-clearance* 20.2 cm<sup>3</sup>/min. and for *creatinine-clearance* 18.5 cm<sup>3</sup>/min.

My contention, that the two clearances vary just the same when determined under identical conditions, is also borne out very beautifully by a study of the authors' diagram of the results obtained in these 50 cases; it is superfluous to detail this, however, because the question is settled by the practical identity of the standard deviations as quoted above.

Before leaving Josephson and Lindahl's paper attention shall incidentally be drawn to the fact, that they obtained an average inulin-clearance in 25 healthy grown up males of 140 cm<sup>3</sup> per min. »This average for the clearance of normal subjects is higher than the values reported by Smith, Golding, Chasis, Richards, Bott, Westfall, Berdal, and Alving and Miller, which were 120—125 cm<sup>3</sup>/min.» It is also higher than the averages for inulin-clearance that were discussed in my first paper in this journal (vol. 118 p. 156), which were 120, 125, and  $122 \pm 20$  cm<sup>3</sup>/min. Josephson's inulin-average is, indeed, somewhat higher than the average creatinine-clearance of the 341 healthy subjects, reported in my *Integrative Natur* etc.» which is  $135.7 \pm 30$  cm<sup>3</sup>/min. All this underlines the fact, emphasized on page 157 of my first paper, namely, that the filtration volumes determined by the inulin-method fall entirely within the range of the

filtration-volumes obtained by the creatinine-method, and that the inulin-volumes do not thus warrant any conclusion that is not warranted also by the creatinine-volumes. This becomes even more obvious from Josephson's and Lindahl's paper. Smith's assertions, that inulin gives a so much lower filtrate volume than creatinine as to warrant the initiation of a new era of renal research, are far from adequate.

Turning now to comparisons between the inulin- and creatinine-clearances, that *have not* been based on simultaneous determinations of the two clearances in the same individuals, I need not again point out, that such heterogenous determinations afford no means of deciding, whether or not the one clearance varies more than the other. I submit the following remarks only to show, that there is *no difficulty in finding series of inulin-clearances that have varied as much or more than the creatinine clearance has varied in other investigations.*

Thus, in a paper by Hogeman, (Svenska Läkartidningen, 1943, vol. 40, nr. 38, p. 2253—64.) 35 healthy grown-up Swedes were examined as far as possibly under standardized conditions; the tests were performed in the morning, the patients fasting; they received  $\frac{3}{4}$ —1 l. water during the hour prior to the inulin-injection, which lasted 4—5 minutes; all blood- and urine-samples were taken at definite, carefully recorded times, great attention was paid to complete emptying of the bladder, catheterization employed whenever necessary, etc. 20 patients received 100 cm<sup>3</sup> and 15 patients 50 cm<sup>3</sup> of a special 10 % inulin solution; in each patient inulin-clearance was determined during three consecutive periods of 20—30 minutes.

*Average inulin-clearance* was 121 cm<sup>3</sup> per minute in the first group of 20 patients and 118.6 cm<sup>3</sup> in the second group, or 120 cm<sup>3</sup> in all the 35 patients. In the different patients *the means* of the three consecutive determinations ranged between 102 and 150 cm<sup>3</sup> per min.; the lowest *separate clearance* recorded was 90 cm<sup>3</sup>, the highest 158 cm<sup>3</sup>. The means thus ranged between 120 cm<sup>3</sup>—15 % and 120 cm<sup>3</sup> + 25 %, a range of together 40 %; the individual determinations may, according to the above, be 32 % higher or 25 % lower than 120 cm<sup>3</sup>/min., a range of together 57 %.

There is no difficulty in finding series of creatinine-determinations where the creatinine-clearances have varied just in the same degree or even less than in Hogeman's inulin-tests.

On p. 451 in my Integrative Natur etc. I have thus a table of 50 creatinine-determinations by Poulsson. The average creatinine-clearance of all the 50 tests is 157.8 cm<sup>3</sup>, the separate means of the 8 experiments, in which the series is subdivided, range between 149 and 170.3 cm<sup>3</sup> per minute; *i.e.* the means of the separate experiments range between figures 5.6 %



lower and 7.9 % higher than the general average (as against Hogeman's —15 % and + 25 %). The lowest separate creatinine-clearance recorded in Poulsson's series is 136 cm<sup>3</sup> (= 13.8 % lower than the general average) the highest is 184 (16.6 % higher than the general average); cf. Hogeman's corresponding figures —25 % and + 32 %.

That is to say, *the range of variations of Hogeman's inulin-clearances is about 2—3 times the range of variation in Poulsson's creatinine-clearances*; it is worth noting, on the one hand that Poulsson's determinations were performed on few subjects, whereas Hogeman examined 35 different persons; on the other hand, all other experimental conditions were standardized in Hogeman's series, whereas they differed somewhat in Poulsson's: 1 liter extra fluid was thus given in some but not in other of the 8 experiments and pituitrin was similarly injected only in some instances etc.

Inulin enthusiasts have repeatedly intimated that the alleged greater constancy of the inulin-clearance is a matter of great physiological importance which, among many other things, would indicate the exaggerated and erroneous nature of the results obtained by Rehberg's creatinine-method. Actually, however, the inulin- and creatinine-clearances vary just the same; different degrees of variability are occasional and due to determination of the clearances under unequal conditions. This conclusion allows us to pass with confidence to a brief discussion of the causes of those variations of the volume of the glomerular filtrate as shown by the creatinine-clearance.

\*                      \*

\*

### The lability of glomerular filtration.

As already mentioned on p. 237 above, everything points, in fact, to the conclusion that glomerular filtration is a rather labil process; this circumstance in itself serves further to negative the alleged greater constancy of the inulin-determinations of the filtrate volume.

The factors most directly connected with the volume of glomerular filtrate are:

- 1) the volume of the renal blood,
- 2) the glomerulo-capillary blood pressure,

3) the colloid-osmotic pressure of the plasma,

4) the intracapsular pressure,

5) the area of the glomerular filtering surface (cf. *Integrative Natur* etc. p. 75—82). It is also possible that the velocity of the blood in the glomerular capillaries, and the time of its passage through them, may be of importance at least under certain circumstances (ibid. p. 76; *Principles*, p. 609—10).

Each of these factors is not only of rather complex nature in itself but is also influenced, in augmenting and restricting ways, by numerous further factors and processes. Space does not permit even mere enunciation here of for instance the various ways in which the renal, and more particularly the glomerular, capillary tonus is subjected to nervous, hormonal, and other chemical influences of renal or extra-renal origin; this is discussed in chapters 6 and 29 of the «*Integrative Natur*» (der renale Kapillartonus und seine Regulation, p. 137—170; *Vasomotor. Natur der Nieren-nerven*, p. 830—49); in fact, the local and general renal capillary tonus influences profoundly both the extension of the glomerular filtering surface, as well as the glomerulo-capillary blood-pressure, and the volume of the blood passing through the glomeruli.

Nor can we detail here the multifarious ways in which changes of all these factors may combine in augmenting or lessening the volume of the glomerular filtrate, nor the many ways in which they may balance and counteract each other. Many particulars as to all this can be found in the «*Integrative Natur*» (p. 75—82, 92—101, 137—170, 234—39, 478—96) as well as in the many special papers mentioned there.

It suffices here to point out, that none among the five principal filtration factors just mentioned is constant, not even *the colloid-osmotic plasma pressure*; it changes a little in the course of the day because of metabolic and digestive processes; it may even change because of the position of the body, as is evident from p. 80 of *Integrative Natur*: Ni and Rehberg found a colloid osmotic pressure of 22 mm Hg in the plasma of a person in bed; it had risen to 27 mm when the same person had been up for 30 minutes. These changes of the plasma's coll. osm. pressure may certainly be small, but it must be recollected from the quoted page, that even a change of no more than 1 mm Hg in itself is quite sufficient.

to augment or lessen the volume of the glomerular filtrate rather much; when a great number of synergistic and antagonistic factors are nicely balanced, as in the case of glomerular filtration, the balance may be rather decidedly pushed towards the one or the other side even by small changes of one factor, unless counterbalanced by an opposing change of other factors.

Turning then to *the volume of the renal blood*, we cannot for a moment maintain the idea of any particular invariability here. Not only is the minute-volume of the heart widely variable under a multitude of conditions, but the various organs of the body compete to very different and variable degrees for the circulating blood. The kidney's chief competitors for the blood are the muscles and the digestive organs; both of these, and especially the muscles, draw heavily and to very different degrees on the common supply of circulating blood. How could the volume of blood, left over for the kidneys, possibly be anything but variable under these circumstances? Even if the renal vessels, by suitable changes of their width, are able to counterbalance these influences to some degree, how could they possibly always counterbalance them precisely?

Actual measurements of the renal blood-supply testify also strongly to the idea, that already the normal renal blood-supply is rather variable. Leaving those measurements aside here, that are based on various kinds of computation, and turning to direct measurements by »Strohmuhrs» and similar methods, we find from the data collected from various authors into the Principles of Renal Function (p. 594—96, cf. Integrative Natur, p. 47), that the kidneys of mammals normally receive between 2—3 g blood per minute and g kidney weight; this figure increases to some 4—6 g in Starling's heart-lung-kidney-preparation, where the kidneys have been deprived of all nerve-supply and where the renal vessels consequently are abnormally dilated.

Now, these figures are *average figures*, the figures actually obtained in the separate measurements are higher as well as lower, and range in a normal animal between c:a 1.5 and 3.6 cm<sup>3</sup> per minute and g kidney; they may occasionally vary even more in both directions, as is very obvious from the quoted instances. The mentioned average is rather a theoretical mean figure from

which actual bloodsupply usually differs. This is well exemplified by the experiments discussed in an earlier paper in this journal (vol. 118 p. 150) where the renal bloodflow was carefully measured in a number of rabbits. In 5 rabbits with perfectly normal renal function it varied between 1.6 and 3.1  $\text{cm}^3$  per minute and kidney weight, averaging 2.3  $\text{cm}^3$ . In 4 rabbits, where certain functional abnormalities had been induced by excessive elevation of plasma creatinine, it varied between 0.8 and 1.2  $\text{cm}^3$ , averaging 0.9  $\text{cm}^3$ .

Turning now to another among the principal factors responsible for the volume of the glomerular filtrate, viz. the glomerulo-capillary bloodpressure, we are again confronted by considerable variability. Actual measurement of this pressure is, of course, exceedingly difficult and has so far only been possible in frogs, where Hayman has measured it in 181 glomeruli by means of an ingenious and most painstaking method, which has been discussed in Principles (p. 278—82) and Integrative Natur etc. (p. 78, 235—37). He concludes, that »glomerular diastolic capillary pressure can on an average be regarded as amounting to 54 % of systolic aortic pressure; it may be only some 8 % of it, but is usually 41—70 % of aortic pressure (11 out of 181 cases).» His results tally well with Landis' measurements, in Krogh's laboratory, of the pressure in certain other capillaries of the frog, where a high capillary pressure also is to be expected (Principles, p. 279, 612—17). Although such measurements, for anatomical reasons, are not feasible in mammalian kidneys, yet they are of interest for these kidneys as well, because it can be shown that only some 20 % of the creatinine in the renal blood is filtered off in the glomeruli (cf. Renal Extr. Rate of Creatinine, this journal vol. 118 p. 146. Integrative Natur, p. 49—50, 245—47); this implies an average glomerulo-capillary pressure about twice the colloid-osmotic pressure of the plasma and about 40—50 % of normal arterial systolic pressure (loc. cit., p. 246).

Now, it is obvious from Hayman's paper that glomerulo-capillary blood pressure is rather variable, and he also emphasizes this conclusion as one of his major results. In individual glomeruli the pressure deviates so frequently and widely from the average 54 %, that this figure becomes a mere theoretical mean indicating glomerulo-capillary pressure in the kidney as a whole under average conditions.

These variations become still more marked whenever the blood pressure is interfered with artificially. Hayman emphasizes that »influences acting on arteriolar pressure (for instance adrenalin, caffein) may influence glomerular capillary pressure to a degree quite out of proportion to their effect on aortic pressure. Under these circumstances the usual correlation between aortic and capillary pressure is in abeyance» (Principles, 281—82). In short, it cannot possibly be disputed, that glomerulo-capillary blood-pressure, the immediate driving force behind glomerular ultra-filtration, is a rather variable factor, indeed.

This conclusion becomes evident also when we take still another of the five principal filtration-factors into consideration, namely *the extension of the glomerular filtering surface*. The area of this surface obviously increases and decreases in extent with the degree to which the glomerular capillaries are open to circulation: opening up or closure of capillaries will also affect the pressure within them. It is in fact *characteristic of the kidneys that only a minority of the glomerular capillaries are open to circulation simultaneously*.

This depends partly on the fact, that a number of entire glomeruli remain closed to the blood; according to Hayman and Starr about 25 % of the total number remain inactive under ordinary conditions in rabbits' kidneys (cf. Principles, p. 261, 500). Of far greater importance in this connection, however, is the fact that, even in the functioning glomeruli, *only a minority of their capillaries are normally open to the blood-stream at one and the same time*. This is evident from examination of several thousands of functioning glomeruli in frogs' kidneys, where a brisk circulation was maintained; it is also evident from the strikingly different appearance of those glomeruli where all the capillaries were artificially induced to open themselves, and from the fact that the phenomenon of a glomerulus throwing all its capillaries open to the blood has only been observed after a special kind of artificial stimulation and has never been observed to occur spontaneously in one of all the thousands of glomeruli examined (Integrative Natur, p. 148—49; Virchows Arch. vol. 284, p. 366—68 and 374—82; Principles, p. 264—71). *That the conditions are most extraordinary, when a glomerulus has opened all its capillaries to the circulation, is also evident from the enormous quantities of filtrate then produced*: quantities at least ten times as large as those, which human glomeruli on an average can be computed to form, have repeatedly been withdrawn from frogs' glomeruli with all their loops open to the blood (Principles, p. 245—57, 297—98). Some stress should be put upon the expression »at least» above, because in addition to the filtrate, collected from the capsules of such glomeruli and

carefully measured in special apparatus, a certain amount of filtrate could as a rule also be observed to leak out from the capsule at the side of the puncture pipette and to stream away over the otherwise carefully desiccated kidney surface. Each sample of filtrate withdrawn was, of course, prior to determination of the volume subjected to repeated and detailed tests for the exclusion of possible admixture of blood, lymph or other fluids (Principles, p. 226—32). In addition to these 16 cases, just referred to, I have even withdrawn somewhat more fluid from 30 other glomeruli with all their loops open, where the tuft became slightly damaged during the puncture operation, so that a certain amount of blood added itself to the filtrate. Counting the blood corpuscles in the sample collected, always showed the blood-admixture to amount to less than 15 % of the sample's volume (Principles, p. 247, 291—92). The increase in volume due to the blood admixture was in other words too small materially to affect the measurement of the volumes of filtrate produced, this especially as some capsular fluid was lost through leakage, in the majority of these cases.

There can in other words be no question as to the fact that the glomerular capillary system is constructed on so liberal a scale that only a minority of its loops normally can be open at one and the same time. There is a great functional reserve of glomerular capillaries in the kidney; this fact shall not be discussed here but is of very great importance in renal pathology (Principles, p. 297—307).

Now, there is one additional fact obvious from microscopical studies of functioning kidneys, namely *that open and closed glomeruli and still more that open and closed capillary loops incessantly change*; especially where circulation is brisk and lively, formerly closed capillaries and anaemic glomeruli can always be seen to open themselves to circulation, and vice-versa (Principles, p. 261—64). *Obviously, this implies variations both in the local glomerulo-capillary pressure as well as in the area of the filtering surface.* I endorse completely the statement by Hayman and Starr (cf. Principles, p. 500), namely, that »wide variations in the number of open glomeruli occur spontaneously and may be produced experimentally. Hence the surface of the glomerular membranes to which the blood has access is variable» (J. exp. Med., 1925, 42, p. 641). This conclusion appears the more justified, if we remember that the variations of the individual glomerular capillaries are incomparably more frequent than those of the entire tufts, with which latter Hayman and Starr were chiefly concerned in their paper.

Nothing much can at present be said as to the last one among the principal filtration factors, *the intracapsular pressure*. It has

neither been possible to measure this pressure directly as yet, nor to compute it under physiological conditions. Nothing is known of this pressure at present, except that it exists and that it is higher in an unknown degree than the tissue pressure outside the capsules. This is obvious from the fact, that the capsules regularly are to be seen in a collapsed state in anaemic glomerules. Tufts with capillaries open to the circulating blood, on the other hand, are always surrounded by the clear space of the distended capsule; when tufts change over from the anaemic to the circulatory state the capsules can actually be seen to distend themselves, and, contrariwise, they can actually be seen to collapse when tufts get anaemic. This clear space of some 10—30  $\mu$  round the tufts enables the operator to puncture the capsules without always at the same time lesioning the tufts and their capillaries.

It is also known, that artificially induced increases of the intracapsular pressure suffice to stop glomerular filtration altogether, if large enough; this is made very evident by a series of technically most accomplished experiments by White (Principles, p. 705—707: Amer. J. Physiol., vol. 90, p. 700—701). In Starling's heart-lung-kidney-preparation this pressure may also rise during zyanidization-experiments so as to upset renal circulation very profoundly (Principles, p. 646—48; Integrative Natur, p. 24). Probably the intracapsular pressure of a functioning glomerulus is normally but a trifle higher than the surrounding tissue pressure.

It is clearly out of the question that a process, such as glomerular filtration, which is influenced by so many different factors, and where the principal component factors are so variable, could possibly be characterised by any greater degree of stability. The question is far more *why glomerular filtration does not vary more in volume than it normally does*. We cannot enter into a detailed discussion of that question here, but the answer is no doubt connected with the fact, that the filtration factors partly influence the filtration process in opposite senses — glomerulo-capillary pressure, for instance, presses fluid out of the blood through the filtering glomerular membranes, while the osmotic pressure of the plasma-colloids and the intracapsular pressure oppose this. Similarly, when one of the principal filtration factors changes, the effect on the filtration may be more or less counterbalanced by simultaneous changes of

other factors with an opposite effect. Ample possibilities for more or less effective mutual equalization are afforded by the intimate interrelations of most of the principal filtration factors, especially as each of them is of a rather composite nature in itself and shares several components with the other principal filtration factors.

*Every process of balancing* — and especially a process of balancing against each other a multitude of everchanging variable objects or factors — *implies, however, a labil equilibrium*, where the balanced matter is continually fluctuating. Similarly, a performing juggler, who balances a high column of objects on his head, maintains its labil equilibrium by incessantly moving his head and body in various directions; he steps backwards and forwards, now to this side and now to the other; the amplitude of these movements and of the swayings of the column varies with the individual juggler and with the conditions of the performance, and varies also a good deal by chance; it increases sometimes relatively much, especially when some detail condition of the performance is changed.

*Glomerular filtration gives throughout, the impression of a process where such a labil equilibrium is implied.* A mere glance at our figures 1—4 (this journ. my 2nd paper) suffices to show, that the volume of the glomerular filtrate fluctuates almost incessantly; these increases and decreases of the filtered volume are as a rule quite moderate and remain well within the range of  $\pm 20\%$  of the average volume filtered; only twice do larger deviations outside this range occur in figures 1—4; larger deviations, however, become more frequent if we turn to a more heterogenous material of determinations, *i.e.* a material where the filtrate volume has been determined in numerous different individuals under a multitude of experimental and physiological conditions (cfr. the 500 determinations in table 3, Integrative Natur, p. 221—26). It is rather immaterial, whether we examine the variability of the glomerular filtrate volumes by means of the creatinine method as in figures 1—4 or by means of the inulin method; the differences, that have been alleged to exist between the two methods as to the degree of variability of the filtrate volumes determined, do on closer scrutiny evanesce quite as much as most other differences alleged to exist between methods that actually agree far more than they disagree.



I have enlarged somewhat upon the variability of glomerular filtration because this variability is really quite an important matter in kidney physiology; it is important in more than one respect, as will become evident from later papers. In this paper, however, attention shall only be drawn to the fact, that *this variability of the filtrate volumes is of some consequence to the excretion of the waste-products, and influences their clearances in a conspicuous manner*; this variability constitutes also a most important reason for the fundamentally different manners in which the excretions of waste-products, on the one hand, and of water and other threshold bodies, on the other, are regulated.

*This variability of the filtrate volume prevents the filtered quantities of any urinary constituent from being strictly proportional to the plasma concentration of the constituent*; this follows from the fact, that the filtered quantity of any filtrable substance equals the product of the filtrate volume and the plasma concentration of the substance. These incessant positive and negative deviations of the filtered quantities from a strict proportionality to the plasma concentrations are by no means always inconsiderable, especially during shorter periods of observation; occasionally, they may even be large. It is easily seen *that the variability of the filtrate volume, in just the same way, renders also all other relations between the filtered quantities and the quantities contained in the blood only approximate.*

### The excretion of urea.

Like the filtered quantities of any other substance *filtered urea equals the product of the filtrate volume and urea plasma concentration*. The variations in the volume of the glomerular filtrate prevent the filtered urea from always being strictly proportional to the urea level of the plasma.

Just as in the case of creatinine, temporary deviations from strict proportionality may be considerable, as is apparent from figures 1 and 2 below. During longer periods the positive and negative short-term deviations, however, counter-balance and equalize each other more or less; as a rule mean urea filtration approaches therefore to a somewhat closer, although by no means strict proportionality to the plasma level of urea; even mean urea filtration may occasionally deviate rather conspicuously from such strict proportionality, as is the case towards the end of the 1st and at the beginning of the 2nd of the experiments represented in the below figures.

1:st Exper. Table 1.

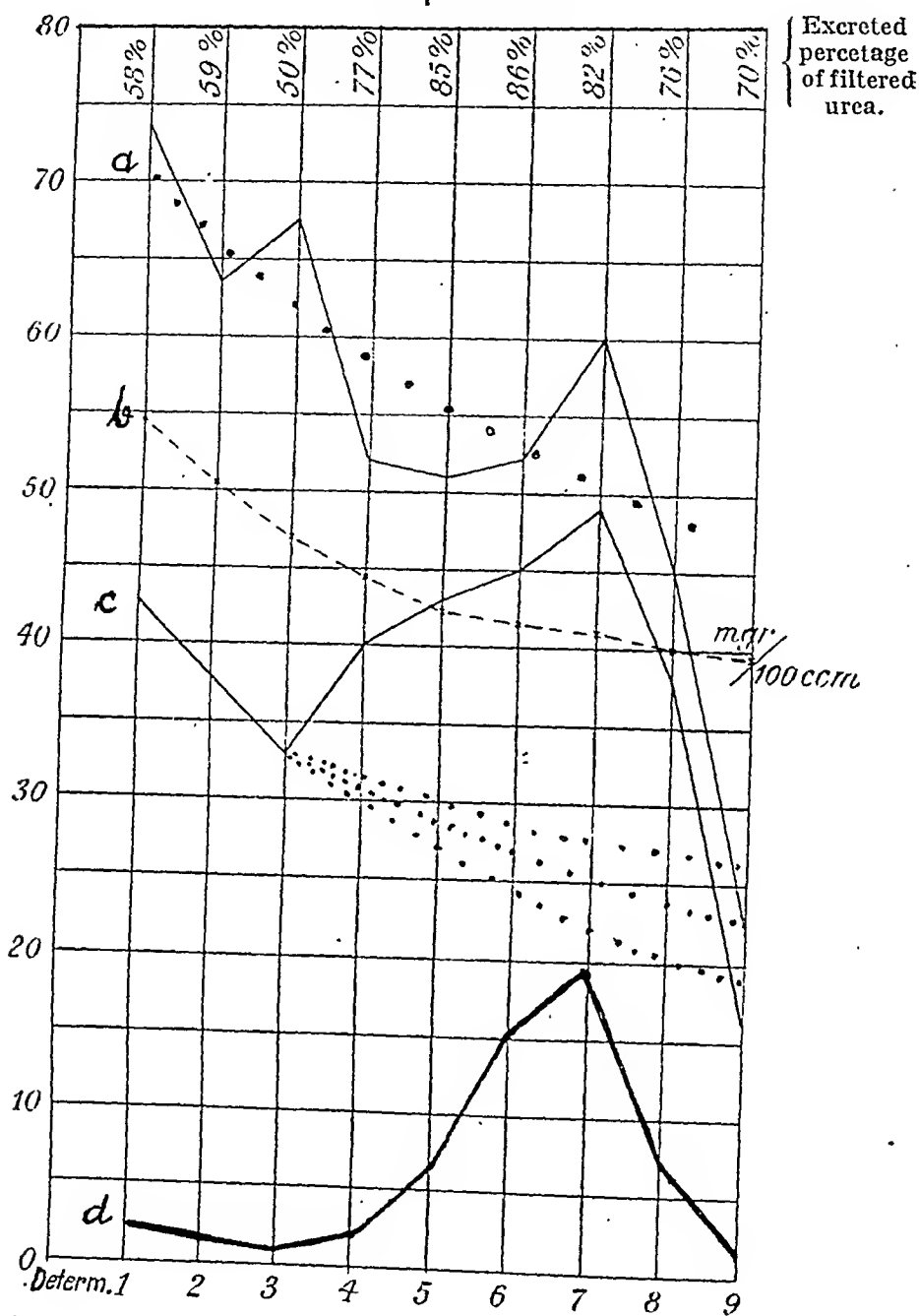


Fig. 1.

Urea excretion in 1:st Exper. of Table 1, cf. this journal vol. 119, p. 62 and fig. 7, p. 72.

a: filtered urica (fulldrawn curve), mg/min. Dotted line: mean urica filtration.

b: plasma urica, mg/100 cm<sup>3</sup>.

c: excreted urica (fulldrawn curve), mg/min. Dotted lines: alternative excretion curves in the case no water diuresis had intervened.

d: water excretion, cm<sup>3</sup>/min.

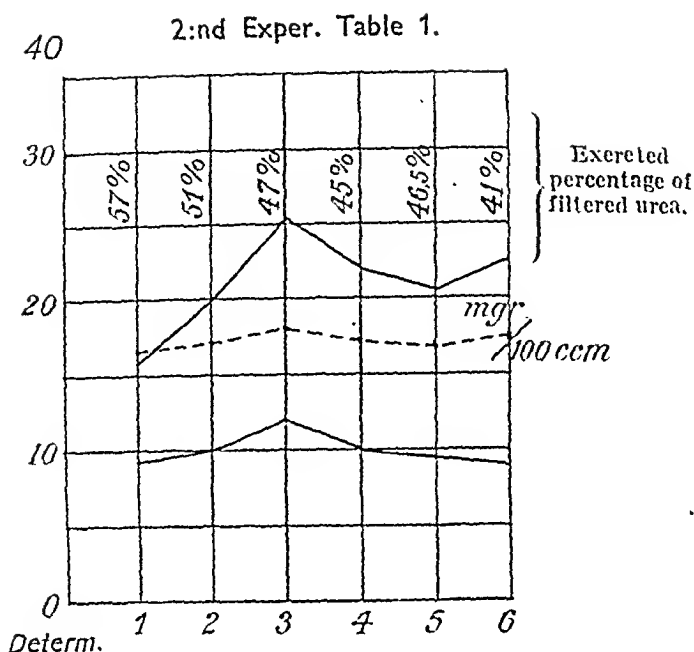


Fig. 2.

Urea excretion in the 2:nd exper. of Table 1, cf. this journal, vol 119, p. 62.

Upper fulldrawn curve: filtered urea in mg/min.

Lower " " " " excreted " " " "

Dotted curve: plasma urea, mg/100 cm<sup>3</sup>.

The excretion of urea differs from that of creatinine in this respect, however, that only a part of the filtered quantity is retained in the final urine, the rest escaping from the tubules during the reabsorption of water. The escaping fraction usually amounts to about 50 % of the filtered urea so long as ordinary volumes of urine are formed (about 1 cm<sup>3</sup> per minute); somewhat more may escape if the urine becomes restricted: thus up to 60 % of the filtered urea escaped from the urine in the experiment of fig. 2, where the urine was sparse (urine volume fell gradually from 0.7 cm<sup>3</sup> per minute at the beginning of the experiment to 0.4 cm<sup>3</sup> at the end). Conversely, considerably less than 50 % of the filtered urea may escape from the urine during copious water diuresis; thus the escaping fraction becomes very much reduced during the strong water diuresis in the first of the above exp.: it remains at or

below 24 % of filtered urea during the whole diuretic period and it falls to 14—15 % during the peak of water excretion (cf. my paper in vol. 119 of this journal. where table 1, p. 62, gives the particulars of the two experiments from which the above figures 1 and 2 are drawn).

Now, *the finally excreted urea* would obviously be proportional to plasma urea, just as urea filtration, if the escaping fraction of filtered urea always remained exactly 50 %. If a certain quantity is proportional to a certain factor, 50 % (or any other definite and invariable percentage of the quantity) is necessarily proportional to that factor as well; the quantity is lowered, absolutely, by being multiplied by that percentage, but the lower quantity is just as proportional to the said factor as the original quantity. Similarly, if the original quantity deviates from a strict proportionality to the said factor, the lower quantity does the same, and it deviates relatively just as much, so long as the lower quantity remains the same fraction of the original quantity. If excreted urea always remained just 50 % of filtered urea, excreted urea would obviously behave just a filtered urea does, and the only difference between the two quantities would be that the one was half the other.

Relations are not quite so simple, however, because excreted urea is not always 50 % of filtered urea, as I mentioned above.

These fluctuations of tubular urea »reabsorption» introduce a further moment of approximation into urea excretion. Urea excretion follows the plasma level of urea in an only approximately proportional manner *not merely because the filtrate volume varies but also because varying fractions of the filtered urea are resorbed by the tubules.*

*Small fluctuations of the reabsorbed fraction of filtered urea* do not, of course, cause the amounts of excreted urea to deviate much more from proportionality to plasma urea than filtered urea does. Small or moderate such fluctuations, indeed, may sometimes cause excreted urea to become more closely proportional to plasma urea than filtered urea; this may occur when filtrative and resorptive fluctuations are simultaneously positive *or* simultaneously negative; *i.e.* when for instance increased filtrate volume and increased filtrative output of urea is balanced by tubular resorption of a higher fraction of filtered urea — *or* when lessened filtration is balanced by resorption of less of the filtered urea. Thus we see in fig. 2, that the amount of excreted urea fairly closely parallels the level of plasma urea, although filtered urea rather fails to parallels

plasma urea during the first half of the experiment and parallels it only roughly during the experiment's latter half.

*Great fluctuations of the reabsorbed fraction of the filtered urea*, on the other hand, will necessarily cause excreted urea to deviate further from proportionality to plasma urea than filtered urea. Such great fluctuations may even temporarily extinguish all proportionality between the excreted urea and the plasma urea.

Thus we see in fig. 1 that urea excretion during the first 3 determinations runs fairly parallel to the falling level of plasma urea. After this, however, a large increase occurs in the urea excretion, although plasma urea continues to fall at a gradually decreasing rate. In order to show, how large a break away this increased excretion is from an excretion proportional to plasma urea, the first part of the excretion curve has been continued by three dotted lines, denoting alternative excretion curves roughly proportional to plasma urea (vide fig. 1). The close resemblance between the two excretion curves for water and urea during the period of water diuresis — during this period these two curves parallel each other rather closely, fig. 1 — indicates, that the sudden large peak in urea excretion is closely connected with the strongly increased water output, i.e. it indicates that the lessened water resorption lessens the escape of filtered urea from the urine back into the blood in the way described (cf. below.).

This increase of excreted urea is large enough to abolish for the time being every semblance of proportionality between the excreted and the plasmatic urea; it is entirely due to the lessened escape of filtered urea from the tubular urine during the very strong water diuresis in the later part of the experiment; a lesser fraction of filtered urea diffuses away from the urine in the tubules, because less water is resorbed and, above all, because the lessened water resorption raises the concentration of the urinary solids, and hence also the diffusion pressure of urea, far less than ordinarily (cf. table 1, column VII, this journal, vol. 119, p. 62: prior to the water-diuresis urea reached concentrations of 2—3 % in the urine, and during the water diuresis urea concentration is always below 0.47—0.64 % in the urine and falls to 0.25 % at the lowest).

Summing up what we have said hitherto, we might say, that *the excretion of urea parallels the level of plasma urea in a somewhat fitful manner*. Not only the fluctuating volume of the glomerular filtrate but also later tubular escape from the urine of varying fractions of the filtered urea may cause urea excretion to deviate from a strict proportionality to plasma urea. Such deviations may be far wider in the case of urea than in the case of creatinine, where deviations only were due to fluctuations of the filtrate volume. There is, on the other hand, no hard and fast rule that urea

excretion should *always* deviate more than creatinine from strict proportionality to the respective plasma level; the two factors making for deviations of the urea excretion may happen to counteract and to balance each other more or less (cfr. above).

Now, these excretory deviations from strict proportionality to plasma urea matter normally very little or not at all to the organism. *Small excretory deviations* are obviously of no importance and even moderate deviations do not nullify the proportionality but only render it somewhat irregular; a conspicuous elevation of plasma urea will *in any case be followed* by at least a marked increase of urea excretion and it *may be followed* by a somewhat more increased excretion than corresponds to the raised plasma level. The second alternative is of advantage to the organism, which only wishes to get rid of its urea, while a sub-proportional excretory increase only retards the excretion somewhat without preventing the elimination of a fair amount of the surplus urea.

*Wide excretory deviations*, on the other hand, are certainly temporarily able to abolish the said rough proportion between plasmatic and urinary urea, but this is normally only to the advantage of the organism, as such wide deviations in healthy kidneys occur only in the direction of increasing the urea output.

As a matter of fact, much more than some 60 % of the filtered urea does not escape from the urine in healthy human kidneys, even when the urine is rather concentrated and rather restricted in volume (cf. fig. 2 above and the corresponding experiment in table 1, this journal, vol. 119, p. 62). It is a pathological phenomenon, if markedly more urea begins to escape, as will be described in my following paper on the excretion in diseased kidneys. The order of the escaping fraction of filtered urea may change a great deal in the opposite direction, however; it may fall to some 25—30 % during slight or moderate water diuresis and to 14—15 % during strong water diuresis; this causes a urea excretion much above what strictly corresponds to the plasma level of urea (cf. above).

### *The tubular »resorption» of urea.*

It only remains to add some few remarks as regards the escape of part of the filtered urea from the urine, the effects of which on urea excretion we have discussed above.

It has long been known, that water diuresis, especially in healthy kidneys, is accompanied by increased output of urea,

the more conspicuously the stronger the water diuresis is. We are not concerned here with the various hypotheses that have been submitted earlier in explanation of this «washing out» of urea, because prior to Rehberg no measurements of the glomerular and tubular prestanda were possible, and all earlier explanations remained therefore necessarily conjectural; the matter was given but little attention, and this «washing out» of urea during water diuresis is barely mentioned and not at all discussed in Cushny's Secretion of the urine (ibid. 2nd edit. p. 90).

The explanation of this «washing out» became evident at once when Rehberg's creatinine-test was first published and quantitative data of the principal partial functions of the kidney became available. Rehberg, who did not otherwise analyze the data obtained, submitted in his first publication a few remarks, however, that render it obvious, that the escape of urea from the tubular urine must be regarded as *a diffusion of urea back into the blood*, and that *the degree of this escape is determined by the degree to which tubular resorption raises the concentration of urea in the urine over its concentration in the blood*. (Rehberg, Biochem. J., 1926, 20, p. 447; cf. Integrative Natur etc. p. 256) His view has not been materially effected by later research, the results of which are best described as mere restatements of Rehberg's conclusions. The often somewhat diffuse, and occasionally somewhat divergent nature of these later statements, is invariably due to the fact, that other authors never have taken the trouble to record or discuss the renal data at all adequately; how many mg of urea the tubules resorb is never, and how many mg the glomerules filter, but exceptionally computed by the later authors; still less have they taken the trouble to compute the degree of urea admixture to the resorbed water (urea percentage in the resorbed water). The later authors have never gone beyond determining the escaping fraction in per cent of filtered urea, which percentage equals the ratio between the clearances of urea and creatinine.

I have reexamined Rehberg's opinions in some detail in my monograph: Integrative Natur der normalen Harnbildung (chapters 9—11), because another author, who based himself on a large but inadequately analyzed experimental material, believed himself justified in suggesting, that the different degrees, to which urea escaped from the tubular urines, were largely caused by varying specific behaviour of the tubular cells

towards the urea. As far as healthy kidneys are concerned, however, this idea becomes altogether unwarranted as soon as one submits the dissenting author's own material to a more adequate consideration and takes account of the data which the author has neglected but which are easy to compute.

With one exception I have found nothing to add to Rehberg's above mentioned view. This exception refers to the question whether a normally minute fraction of the filtered urea escapes from the urine, not as an admixture to the reabsorbed water, but as an admixture to the electroactive solutes that are reabsorbed independently in the proximal portion of the tubules (the water is reabsorbed lower down in the tubules). This small fraction of urea, however, is normally too minute to be of any importance whatever; only under certain abnormal conditions may it increase and cause highly interesting clinical phenomena not without therapeutical importance (cf. *Integrative Natur*, chapter 13 and the additional remarks p. 1135—36).

Otherwise I concur completely with Rehberg as to the tubular «resorption» of urea. To sum up, the tubular walls offer a very determined resistance to the escape of filtered urea back into the blood; yet they cannot prevent it altogether, as urea has a very small and easily diffusible molecule, and as tubular water-resorption usually condenses the urine so much, that urea in ordinary urines reaches a concentration of one or several per cent in spite of the escape of about half the filtered urea. This high concentration implies a very high diffusion pressure of the small urea molecules; already a one-per-cent solution of urea has an osmotic pressure of 3.7 atmospheres. When urea and water attract each other with a force of this high order, it is certainly no wonder, that it is impossible for the water-resorptive tubular cells to separate urea and reabsorbed water completely from each other, *i.e.* some urea will get admixed to the water reabsorbed. It is also obvious, that the degree of this admixture will decrease, when the tubules withdraw less water from the urine and thus concentrate its solids less.

Thus we see from column XII, table 1 (this journal vol. 119 p. 62) that the admixture of urea to the reabsorbed water during the formation of ordinary volumes of urine amounts to some 7—10 mgm per 100 cm<sup>3</sup> in one experiment and to 20—23 mg per 100 cm<sup>3</sup> in the other experiment; that is to say, it amounts to about half the simultaneous concentration



of urea in the plasma, the lower figures corresponding to a plasma urea of 16—18 mg/100 cm<sup>3</sup>, the higher to a plasma urea of 40—50 mg/100 cm<sup>3</sup>. The admixture falls to about  $\frac{1}{4}$  of its earlier order during incomplete water reabsorption during intense water diuresis. There is conversely a tendency for the degree of the urea admixture to increase, when water is reabsorbed more completely than ordinarily during the formation of sparse and concentrated urines, but this tendency is considerably less marked than the opposite tendency during incomplete water-reabsorption (cf. above). The difference between the two tendencies is apparently due to the fact, that increases in the concentration of the urine require resorption of ever smaller additional volumes of water, the further the reabsorption progresses, and the more concentrated the urine becomes. The relationship between the degree of urea admixture to the reabsorbed water *and* the diffusion-pressure or concentration of urea in the urine cannot be expressed by a straight line but is also influenced by the very different amounts of water that have to be reabsorbed in order to condense the remaining solution 2, 4, 8, 16, 32 times etc.

\*            \*  
                 \*

The subjects, discussed above, will be concluded in a following paper in this journal by some remarks concerning the clearance of various urinary constituents.

---

My preceding papers in this series:

I. Inulin as a substitute for creatinine in renal tests. This journal, vol. 118, p. 114—62.

II. The importance of adequately recorded results in Rehberg's Kidney test. *ibid.* vol. 119, p. 57—102.

#### IV.

### The clearance of various urinary constituents with special regard to certain particulars of their renal excretion.

By

GÖSTA EKEHORN.

Stockholm.

(Submitted for publication September 13, 1944).

However heterodox my remarks in the preceding paper may appear to many renal workers, they are *confirmed by everyday experience as regards the clearances of various substances*. The preceding examination both of the creatinine and the urea excretion, as well as of the differences existing between this excretion and that of water and other threshold-bodies has, in fact, led up to conclusions, which entirely conform to the characteristics of these clearances, to generally accepted experimental procedures, and to obvious clearance differences between water and threshold-bodies, on the one hand, and waste-products like creatinine and urea on the other.

#### *The clearance of creatinine.*

If creatinine excretion were strictly proportional to the plasma level of creatinine, the quotient  $\frac{U \cdot C_u}{C_p}$  would obviously and necessarily have a constant value ( $U$  designs the volume of the urine,  $C_u$  and  $C_p$  the urinary and plasmatic concentrations of creatinine); this quotient, however, denotes also the clearance of the

substances with the concentrations  $C_u$  and  $C_p$  (cf. this journal vol. 118 p. 115).

Now, the average creatinine clearance and the range of its usual variations are denoted by the figures  $135.7 \pm 30 \text{ cm}^3$  (ibid. p. 156—57). There is obviously no question of a constant clearance nor of a creatinine excretion strictly proportional to the plasma level of creatinine. Even large variations may be met with now and then, even in the same individual, yet such large variations are normally more or less occasional phenomena; the clearance remains as a rule within the limits mentioned, its exact magnitude varies, but it maintains on the whole a general order of magnitude which is quite characteristic for creatinine and different

from those of other substances. That is to say, the quotient  $\frac{U \cdot C_u}{C_p}$  does not change out of all proportion to its usual order but retains, notwithstanding its variations, a characteristic general order of magnitude. *That* the excretion of creatinine is approximately proportional to the level of the plasma creatinine *and that* the clearance of creatinine normally is of a characteristic general order of magnitude but by no means is constant — these two statements, indeed, are but different ways of describing the same thing; these characters of creatinine clearance are universally known, and this removes our earlier description of normal creatinine excretion from the sphere of things still debateable.

It was stated in my preceding paper, that *the volume variations of the glomerular filtrate* are the reason why creatinine excretion more or less deviates from strict proportionality to plasma creatinine; this statement is warranted by the fact, that creatinine clearance and its variations are used for measuring the filtrate volume and its variations. When creatinine normally is neither secreted nor reabsorbed by the tubules, the filtered and the finally excreted quantities of creatinine are equal (cf. this journal, vol. 118 p. 115—16);  $F$ , the filtrate volume, is therefore equal to creatinine clearance according to the formula

$$F = \frac{U \cdot C_u}{C_p} = Cl$$

If  $F$  did not vary in this formula, the above quotient, *i.e.* the clearance, would remain constant, and the amount of excreted creatinine in the urine,  $U \cdot C_u$ , would necessarily remain strictly proportional to  $C_p$ . Hence, the variations of  $F$  are the reason why the excretion of creatinine is not strictly proportional to the plasma creatinine, and why the creatinine clearance varies.

All the above applies to any substance that is neither secreted nor reabsorbed by the tubules. That is to say, the excreted amounts are approximately proportional to the plasma level, and this conforms to the clearance of such a substance. Indeed, the authors of the inulin-school, who attack Rehberg so fiercely, attempt to measure the filtrate volume and its variations in exactly the same way by means of the clearance of inulin, which *they* regard as being neither secreted nor reabsorbed by the tubules; indeed the above formula and its implications apply to every substance not so secreted or reabsorbed.

\*            \*            \*

### *The clearance of urea.*

Turning now from creatinine to urea, we need not waste many words on the fact, that our earlier description of urea excretion is entirely congruent to well-known characteristics of urea clearance. Except during more or less intense water-diuresis, the excretion of urea is roughly proportional to the level of plasma urea, but the proportionality is on the whole even more approximate than in the case of creatinine; this is due to the fact, that the excretion of urea in addition to the fluctuations of the filtrate volume is subjected to a further variable factor with an approximating influence, namely varying escape of urea from the tubular urine during the process of water reabsorption. Just as in the case of creatinine, the fact that urea *has* a characteristic clearance denotes a certain degree of proportionality between its excreted and its plasmatic amounts; the fact, that this clearance may vary relatively more than that of creatinine, denotes that urea excretion is even less strictly proportional to the plasma level than creatinine. It was also emphasized, that urea excretion during intense water diuresis increases quite out of proportion to plasma urea, *i.e.* the ordinary rough proportionality is temporarily annulled; this is reflected in the

clearance of urea, which during intense water diuresis increases from its normal and characteristic order of about half the creatinin clearance so as to come quite near the latter;

Thus in table 1 (this journal vol. 119 p. 62) urea clearance increases during the intense water diuresis of the first experiment to maximally  $120 \text{ cm}^3$  per minute, which is rather near simultaneous creatinine clearance,  $146 \text{ cm}^3$ , and quite within the range of variations of the latter,  $137 \pm 30 \text{ cm}^3$ .

The clearance affords also a simple, obvious, and generally used method for differentiating between such excretion- and clearance-fluctuations of urea that are due to variations of the filtrate volume, and such fluctuations that are caused by varying tubular reabsorption; fluctuations of urea clearance that correspond to similar and simultaneous fluctuations of creatinine clearance are due to the first mentioned, and non-corresponding fluctuations are due to the last-mentioned cause.

The fact, *that* tubular resorption of urea normally is due to admixture of urea to the reabsorbed water, *and that* it varies with the latter regardless of the urea's own excretory situation requires no special discussion here. Nor does the fact, that the renal tubules do not reabsorb urea actively require any special explanation; they reabsorb water actively, but are, according to the reasons mentioned and referred to in my preceding paper unable to prevent all admixture of urea to the reabsorbed water.

\* \* \*

*Water and solid threshold-bodies have no specially characteristic clearances.*

When the excretion of irresorbable and of badly resorbable substances normally is so closely connected with their clearances, matters must be very different as regards the highly resorbable threshold-bodies and the water. In preceding papers (this journal, my 2:nd and 3:rd papers) we have drawn attention to the fact, that the high tubular resorbability of water and threshold-bodies profoundly influences their excretion and renders it very different from that of urea and creatinine. One principal point of difference is, that the very high tubular resorbability of water and threshold-

bodies gives to the tubules a dominating, indeed, a well-nigh exclusive influence as regards the regulation of their excreted amounts; the influence of glomerular filtration on their urinary output is in other words correspondingly reduced; this means, that their urinary output becomes independent of that partial renal process, glomerular filtration, the rate of which maintains an approximate proportionality to the plasma level of the urinary constituents; glomerular filtration of for instance NaCl equals the product of the filtrate volume and the plasma level of NaCl, *i.e.* it follows a quite similar formula as the filtration of, for instance, creatinine, and the filtered amount varies therefore in rough proportion to the plasma level.

The high tubular resorbability of the water and the threshold bodies is further closely connected with another phenomenon, that also contributes to prevent their excretion becoming proportional to their plasma concentrations. Their high tubular resorbability renders their urinary excretion far less complete relatively to the amounts in which they are contained in or supplied to the blood, *i.e.* their Renal Extraction Rates will be far lower than those of the waste-products. The very high tubular resorbability of water and solid threshold-bodies will obviously also prevent their excretion at all, or will at least reduce it to the barest minimum (water), whenever their content in the blood tends to fall below certain levels, *i.e.* there will be certain thresholds; the excretion will be regulated according to whether or not, and how far, these substances exceed their thresholds in the plasma. Their excretion cannot in other words be proportional to their amounts or percentage in the plasma, but relates instead to another and more complicated phenomenon, namely to whether and how far their contents in the plasma exceeds the threshold-level.

*These particulars are also clearly reflected as regards clearance.* The excreted amounts of water and threshold-bodies not being proportional to their amounts or percentages in the blood, *their »clearances» can have no, even approximately, definite order of magnitude;* it follows from the earlier formulas *that the clearance of a given substance can be constant only when the urinary output of this substance is strictly proportional to the plasma's contents of this substance, and that the clearance can be of a characteristic*

general order of magnitude *only when* the output remains approximately proportional to the plasma's contents of the given substance.

It is obvious at once that water and solid threshold-bodies — in contrast to, for instance, urea and creatinine — are *not* characterized by clearances which, although somewhat variable, yet retain a characteristic general order of magnitude.

Thus we saw in table 2 (this journal, vol. 119 p. 64) that the urinary output of chlorine varies between a minimum of 2.24 mg per minute in the 1st and a maximum of 40.2 mg in the 2nd experiment; the corresponding plasma concentrations are 367 and 398 mg of chlorine per 100 cm<sup>3</sup>; this gives »clearances» of 0.0061 and 0.1 cm<sup>3</sup>. When chlorine »clearances» thus may vary as 1: 16 in the normal kidney, it is, of course, impossible to speak of any characteristic clearance at all. Indeed, chlorine clearance may vary much more even in the normal kidney, because 40 mg chlorine per minute is far from a maximal excretion, and chlorine may, on the other hand, disappear altogether from the urine. The fact, that the »clearance» is very low, is no special characteristic of chlorine clearance but applies to the »clearances» of water and all threshold-bodies and is due to the fact that all these substances have so low Renal Extraction Rates (cf. my former papers).

Similarly, the urinary output of water varies in the same table between 0.92 and 17.6 cm<sup>3</sup> per minute; it varies between 0.44 and 19.25 cm<sup>3</sup> per minute in table 1 (this journal, vol. 119 p. 62); neither of these figures represents the possible minimum or maximum of renal water output. We will obtain clearance-figures that vary in proportion as 1: 40 if we divide these water-outputs by the percentage of plasma water, which is always very near 100 %. The »clearances» figures for water will be no less variable and will still fluctuate in the most extraordinary manner, if instead we divide water-outputs like the above by the volume of the renal blood, because this volume may vary a great deal, and it varies in accordance with a multitude of hemodynamic conditions with but little or no direct bearing on the exigencies of renal water excretion (cfr. my preceding paper in this journal.)

In short, *water and solid threshold-bodies have no specially characteristic clearances*; subject to the fact, that these clearances always remain very low, they are however variable; they are in fact too variable and uncharacteristic to be of any use as a means to measure and study the renal excretion of either the water or the solid threshold-bodies.

These very significant differences between water and threshold-bodies, on the one hand, and urea, creatinine etc., on the other, have so far been recognized only very inadequately in renal rese-

arch-work. They have been recognized only in the respect, that no serious attempt has ever been made to use the »clearances» of water and solid threshold-bodies as a means of studying their renal output. It has not been understood, however, that the irrelevance of these clearances implies that the excretion of water and solid threshold-bodies is regulated in a very special manner, profoundly different from that of urea, creatinine etc. This misunderstanding is very obvious from all that we said in a preceding paper concerning the almost universal neglect of the tubular data in studies of the excretion of water and other threshold-bodies (this journal, vol. 119 p. 57).

\*            \*            \*

This somewhat incomplete realization of what is implied in the question as to whether a given substance has a characteristic clearance, has caused many further phenomena to be misunderstood.

The fact, that, for instance, the clearance of inulin is rather independent of inulin-concentration in plasma, has thus been commonly hailed by the inulin-enthusiasts as something quite peculiar to inulin and profoundly characteristic of a substance neither secreted nor reabsorbed by the tubules (cf. Hogeman, Svenska Läkartidningen, vol. 40, Nr. 38, Sept. 1943, p. 2254). As a matter of fact, such independence of the plasma level applies to *the clearance of any substance, the renal excretion of which tends to be proportional to its plasma concentration*. This is but a simple consequence of the formula for clearance

$$Cl = \frac{U \cdot C_u}{C_p}$$

If the numerator tends to be proportional to the denominator in the above expression, the whole quotient (= Cl) tends to assume a constant value whatever the absolute order of the denominator, i.e. the clearance tends to be the same, whatever the plasma level of the substance; this is even more the case, the stricter, i.e. the less approximate, the said proportionality is.

This phenomenon may be quite obvious even in the case of urea, where this proportionality of the output to the plasma level is far from precise. Thus we see from table 4 on p. 146 of my paper in vol. 118 of this journal, that the Renal Extraction Rate of urea — and hence also urea clearance (cf. *ibid.* p. 143—50—52) — conforms



to quite the usual order in a series of rabbits where plasma urea was raised by urea-injections to almost 150 mg./100 cm<sup>3</sup>. This agrees entirely with what has been pointed out above, namely, *that* the clearance of urea, *and that* the proportionality between urea urinary output and plasma level, generally are not much affected in the normal kidney unless the urine becomes very abundant and dilute which was not the case in this experiment.

Indeed, *this independence of the clearance of the plasma level applies also to creatinine*, unless its level is raised so excessively that the kidneys become poisoned and the renal tubules become unable to withstand the enormous diffusion pressure of the creatinine in the urine and allow some of it to escape back into the blood; this, of course, depresses creatinine clearance (cf. this journal, vol. 118, p. 143—50—52).

It must be recollected that with plasma creatinine raised to 100 mg/100 cm<sup>3</sup>, urinary creatinine would get a concentration of over 12 %, if no creatinine escaped from the tubules, and if the usual 124/125—134/135 of the filtered water was reabsorbed; the osmotic (diffusion) pressure of a 12 % creatinine solution is about 20 atmospheres.

Smith's own experiments, extensively discussed in the quoted paper, show, however, that this depression of creatinine clearance *first sets in at plasma creatinine concentrations of about 75 mg per cent, i.e.* at concentrations that are at least a 7—10-fold multiple of the creatinine concentrations used in Rehberg's test, which always are below 10 mg/100 cm<sup>3</sup> in healthy kidneys, and which only in severely diseased kidneys occasionally may rise to 12—16 mg, (cf. the tables in my *Integration Natur der norm. Harnbildung*). On page 134 of the paper in vol. 118 of this journal, Smith's own detailed table covering the effect of the level of plasma creatinine on creatinine clearance has been reprinted. Smith's own records show that *creatinine clearance becomes depressed first at 75 mg per cent of plasma creatinine and that it remains altogether unaffected at creatinine levels of for instance 13—14 and even 30—44 mg/100 cm<sup>3</sup>.*

I utterly fail to understand how the phenomenon, that clearances, except under special circumstances, are rather independent of the plasma level, can possibly be held to be a phenomenon specific to inulin. It is also exceedingly surprising to find this pheno-

phenomenon marshalled as a reason showing that inulin should be more suitable than creatinine as a test-substance in Rehbergian tests; this is especially astonishing, because experiments by the inulin-propagandists themselves clearly show, that this same phenomenon applies to creatinine as well, except under conditions that have no bearing whatever on the conditions of Rehberg's creatinine-test.

All this compares in a remarkable manner with the most surprising ways in which other alleged advantages of Smith's Inulin-method have been stated (cf. my earlier remarks in this journal, vol. 118 p. 114—61 and vol. 119 p. 57).

Other not infrequent misunderstandings of clearance questions, however, are not specific to the inulin-papers. Such a misunderstanding is for instance the idea, *that urinary substances, which are actively or passively reabsorbed by the renal tubules, necessarily should be largely influenced by different degrees of water reabsorption and water diuresis, just as urea is.*

Now, one thing is obvious from my monograph »Über die Integrative Natur der normalen Harnbildung« (cf. *ibid.* p. 1099—1103, 1197—99, 1275—76, and numerous other places quoted there) namely, that water, on the one hand, and most urinary solids, on the other, are reabsorbed in different portions of the renal tubules: the solids in the *first*, and the water in the *lower portions* of the tubules. Urea is rather an exception from the other solids, in so far as its normal tubular resorption almost entirely is due to urea becoming admixed to the reabsorbed water (cf. my 2<sup>nd</sup> & 3<sup>rd</sup> papers). The tubular resorption of most other solids is as a rule influenced much less, or hardly influenced at all, by tubular water reabsorption; it is a distinct pathological phenomenon if they begin to be so influenced to any more conspicuous degree. The reabsorption of solids in the proximal tubular portions being independent of water (and urea) reabsorption lower down, there is no reason, why tubularly reabsorbed solutes should resemble urea in its dependence upon tubular water reabsorption and urine flow.

This applies both to the normally reabsorbed solutes as well as to experimentally introduced substances, such as the many plasma-foreign carbohydrates which have been studied by Smith and his followers. It is obvious both from the Smithian papers as well as from my earlier remarks in vol. 118 of this journal, p. 123—30,

*that* these foreign carbohydrates are subjected to a certain degree of tubular reabsorption after having been filtered in the glomeruli, *that* they are reabsorbed by the tubular mechanism normally reabsorbing filtered glucose, *and that* there is a certain competition between the glucose and the foreign carbohydrates during this resorption. It is also evident from pages 308—09 and 1036 of the »Integrative Natur» that the resorption of glucose occurs in the most proximal portion of the renal tubules, *i.e.* that glucose reabsorption is quite separated locally from the water reabsorption lower down in the tubules. Hence it is only to be expected, that the tubular reabsorption of these carbohydrates shall be independent of water reabsorption and that their renal excretion shall be independent of the volume of the urine; this is also the case.

Although a good deal still remains to be added to the above remarks concerning the excretion in normal kidneys of certain waste-products and certain body-foreign substances, space does not allow further expostulations. My next paper in this journal will be concerned with the excretion of waste-products in some pathological conditions.

\*            \*            \*

*Discussion of this and of the preceding paper.*

The degree of tubular reabsorbability of a given urinary constituent, its Renal Extraction Rate, and its general level in the plasma are all closely interrelated phenomena, as was emphasized in my preceding paper in vol. 120 of this journal, p. 227). Thus, when tubular resorbability of a urinary constituent is of a high order, the R.E.R. becomes low, and the plasma concentration of this substance is maintained at a high level relatively to the quantities in which this substance is supplied to the blood by the food and/or by the metabolic processes of the body.

These phenomena, further, are closely connected both to the thresholds of the highly reabsorbable urinary constituents, as well as to several other particulars of their renal excretion.

On the other hand, *the low tubular reabsorbability of other urinary constituents* (waste-products, a number of artificially introduced

plasma-foreign substances etc.) is responsible for their high Renal Extraction Rates, for the maintenance of their plasma concentrations at low levels, and for several other particulars of their excretion. Chief among these particulars is the fact, that the low resorability of these substances implies that the tubules, as a rule, are unable to influence their excretion to a dominating degree. The glomerular output of these substances not being profoundly altered by subsequent tubular activities, the glomerular output and its variations will thus normally dominate the urinary excretion of these substances more or less; this makes the excretory regulation of these substances in several important respects very different from that of the water and the solid threshold-bodies.

*The glomerular output* of any given urinary constituent equals the product of the volume of the glomerular filtrate and the constituent's plasma concentration; *a safe method to measure the filtrate volume is thus essential* to every discussion of the glomerular output of any urinary constituent. I have therefore in my preceding paper stated the reasons showing, that Rehberg's creatinine-test affords such a method in the case of the normal kidney; the reasons submitted by other authors against this view and alleged to show that inulin is preferable to creatinine for this purpose have been discussed in my earlier papers in this journal and found to be altogether unwarranted.

I have also (preceding paper) examined the question, whether or not the creatinine- and the inulin-methods differ as to the degree of variability of the filtrate volumes determined; contrary to what often has been alleged by the inulin-enthusiasts, compatible determinations show decidedly that the determined volumes vary just the same in the two methods.

In the preceding paper I discussed briefly *the principal physiological factors influencing the volume of the glomerular filtrate*; I emphasized also, that glomerular filtration is a labil process; it is subject to incessant positive and negative variations due to a multitude of hemodynamic conditions, that have no or but slight and indefinite connections with the exigencies both of urinary excretion in general as well as of the excretion of particular urinary constituents.

*In normal kidneys the urinary creatinine equals the quantity contained in the glomerular filtrate.* The filtered creatinine quantity being the product of the filtrate volume and the plasma concentration of the creatinine, *the filtered* and hence also *the finally excreted creatinine is more or less proportional to the plasma level of creatinine*, and would be strictly proportional to that level, if the filtrate volume always remained the same. As this volume varies more or less in positive and negative directions, the filtered and the finally excreted creatinine-amounts display corresponding positive and negative deviations from a strict proportionality to the plasma creatinine level; *i.e.* the proportionality is only approximate. These deviations from a strict proportionality may be considerable occasionally; they largely neutralize each other during longer periods of urinary formation, however.

This somewhat approximate nature of the regulation of the urinary output, however, is normally a matter of no consequence to the body in the case of urinary constituents of low tubular resorbability. Their low tubular resorbability renders their Renal Excretion Rates so high, and their general plasma levels so low, that the precise level does not matter in the least as long as this low general order of their plasma concentrations is maintained.

What has been said above concerning the filtered (and excreted) amounts of creatinine applies also to *the filtered quantities* of any urinary constituent; subject to one exception, it would apply also to *the final excretion of all urinary constituents of low tubular resorbability*; the exception is due to the fact, that the tubules as a rule reabsorb a somewhat varying fraction of their filtered quantities.

Now, if the reabsorbed fraction was constant, instead of being variable, and if the finally excreted quantity thus always represented a % of the filtered amount of a given substance, the excreted quantity would obviously be just as approximately proportional to the plasma level of the substance as the filtered quantity is; the excreted quantity would be a *lower proportion* of what the plasma contains of this substance, but its *proportionality* to the plasma level would be of just the same degree of exactitude as that of the filtered quantity; whenever the latter deviates from a strict proportionality, the excreted amount would deviate just as much. The only differences to creatinine excretion would then be, *that* the finally excreted quantity represents a lesser fraction of what the plasma

contains of the substance (that the R. E. R. is lower than that of creatinine) and that the general level of the substance in the plasma is higher than that of creatinine relatively to the quantities supplied to the blood.

The fact, that the tubularly reabsorbed quantities are *not constant fractions of the filtered quantities*, introduces in the case of the badly resorbable urinary constituents a further reason, why their excreted amounts may deviate from a strict proportionality to their plasma levels.

That is to say, their *filtered amounts* may deviate from a strict proportionality to their plasma levels, because the volume of the glomerular filtrate varies. In addition to this, somewhat varying fractions of their filtered amounts may be reabsorbed by the tubules, and this *may* cause their *excreted amounts* to deviate still more from a strict proportionality to their plasma levels; their excreted amounts *may* do so, but they *may also* deviate *less* than the filtered amounts from such a strict proportionality, which latter occurs when filtration and reabsorption both increase or both decrease at the same time (cf. my preceding paper).

In my preceding paper I went more particularly into these matters in the case of urea, the tubular reabsorption of which already normally is more variable than is the rule among the urinary constituents of low reabsorbability. We saw amongst other things, that the variations of urea reabsorption must reach a certain order of magnitude in order to influence the final urea excretion in any more conspicuous manner. We saw also, that in the normal kidney this occurs especially when the urine becomes abundant and dilute, and that urea reabsorption otherwise did not, and could hardly, vary sufficiently in the normal kidney to cause final urea excretion to deviate very far from proportionality to plasma urea level: the usual small variations of urea reabsorption might as well counteract as they might somewhat augment the influence of the filtrative variations; urea output could thus be *somewhat more* as well as *somewhat less* strictly proportional to the plasma level than creatinine output. Only during intense water diuresis does urea reabsorption vary sufficiently to put the usual approximate proportionality between urea excretion and urea

plasma level into temporary abeyance; this, however, is only to the advantage of the organism, as more urea is got rid of than otherwise would be the case.

The reasons for this close dependence of urea reabsorption upon the water output were contained in the fact, especially emphasized already by Rehberg in his original paper of 1926, namely, that *urea diffuses away from the tubular urine as an admixture to the reabsorbed water*; the water-reabsorbing portions of the tubules are unable to separate the urea completely from the reabsorbed water; the reasons for this and for the fluctuations of urea reabsorption, when water reabsorption varies, are fairly obvious. We have briefly returned to urea reabsorption in the preceding paper in order to point out, that this dependence of urea upon water-reabsorption is something rather peculiar to urea, which must by no means be held also to characterize the tubular reabsorption of other substances, an otherwise not uncommon mistake.

\*            \*            \*

The present paper is chiefly concerned with the question, how far my *earlier description the excretion of of urea and creatinine conforms* to our knowledge of *their clearances*. This conformity is so close and detailed, that my earlier description amounts in fact to a restatement of this knowledge in somewhat different terms. This close conformity is due to the fact, that the very formula for a given substance's clearance,

$$Cl = \frac{U \cdot C_u}{C_p}$$

actually denotes, *that* the excreted amount (the product of the urine's volume  $U$  and the urinary concentration of the substance,  $C_u$ ) is proportional to the plasma concentration of the substance  $C_p$ , *that* this proportionality can be a strict one only if the clearance of the substance,  $Cl$ , remains constant, *that* the proportionality is only approximate when  $Cl$  varies in a moderate degree, *and that* this approximate proportionality is annulled if  $Cl$  varies widely.

The facts, *that the clearances of urea and creatinine are not constant, that the clearance-variations with one exception are small enough in the normal kidney to allow these clearances to retain a certain general order or magnitude characteristic of the particular substance, and that urea clearance moves outside this characteristic order and approaches that of creatinine-clearance in the exceptional instance referred to (intense water-diuresis when the usual proportionality between urea-output and plasma urea is suspended)* — these facts remove our earlier statements concerning the approximate proportionality between the urinary output of urea and creatinine and their plasma levels from the sphere of debateable matters.

The statement, that the deviations of this output from a strict proportionality to the plasma level is due to fluctuations of the volume of the glomerular filtrate or to varying tubular reabsorption — this statement also is most obviously connected with evident applications of clearance-questions and with the generally employed clearance-methods.

Moreover, the circumstance *that all the discussed characteristics of normal urea- and creatinine-excretion are comprised in the formula for their clearances and are decisively connected with the fact, that their clearances, although variable, yet retain a characteristic general order of magnitude* — this circumstance establishes at the same time conclusively, *that all other substances with similarly characteristic clearances are excreted in the same manner.*

Those endless and confused discussions as to how the kidney excretes every normal, pathological, or artificially introduced urinary constituent, are thus rather superfluous in the case of substances with characteristic clearances. The very fact, that such a substance has a characteristic clearance, settles the main questions as to how it is excreted by the kidney. Only subsidiary problems are, indeed, still open to discussion, as for instance *whether* the deviations of the urinary output of such a substance from a strict proportionality to its plasma level are due to glomerulofiltrative or to tubulo-reabsorptive causes, *and whether* resorptive variations are connected with varying resorption of water as in the case of urea, or connected with resorptive processes in other portions of the tubules etc. Rehberg's creatinine-method,



judiciously used, gives wide opportunities for elucidating such details.

It is very surprising, that the above rather obvious matters have been so largely overlooked in the renal literature. In spite of a fairly comprehensive knowledge of physiological kidney papers, yet I cannot recollect ever to have seen even the almost axiomatic fact commented upon however briefly, namely that the renal excretion of a substance with a characteristic clearance implies an excretion approximately proportional to the plasma level of the substance. Still less has due regard been taken of the many detail implications of the clearance-formula and -problems; the consequence of this is, that even the most banal correlated phenomena may be seriously misunderstood; as an instance of this, the opinion of the inulin-enthusiasts may be quoted, namely, that it is specifically peculiar to inulin, that its clearance is independent of its plasmy concentration.

Still more surprising, than this inadequate consideration of what a characteristic clearance implies, is the fact, however, that even the most modern renal literature has quite failed to take the circumstance into consideration, *that numerous and exceedingly important urinary constituents* (water and solid threshold bodies) *have no specially characteristic clearance*. Although it therefore is impossible to study the renal excretion of water and threshold-bodies by means of their clearances, yet nobody has inquired, whether this striking difference between water and threshold-bodies, on the one hand, and waste-products and plasma-foreign substances, on the other, does not also denote a profoundly different regulation of their urinary output; this is also the case, as even the most preliminary analysis of properly computed tables of renal data renders very evident. Nor has the current physiological kidney literature concerned itself the least with the evolution of any acceptable methods for studying the excretion of water and thresholdbodies; the methods almost universally employed compare with examination of the heart by means of so badly prepared electrocardiograms, that every particular except the P-waves is missing; indeed, this comparison is no overstatement, rather the contrary.

All this is very surprising, and would be still more so, did not

everything point to the conclusion, that the rules of quantitative research have not been generally understood as yet in renal physiology; this branch of science has until but comparatively recently remained in so confused a state that not even the principles of renal action were definitely known, nor could any renal partial process be safely studied even qualitatively, not to mention quantitatively. The rules of quantitative analysis are therefore still observed but very imperfectly in the greater part of the physiological kidney literature; thus we saw from the critical remarks in my first and second papers in this journal that important, indeed essential items, both of the problems examined as well as of the experimental results actually obtained, frequently were quite disregarded with detrimental effects as to the validity of the conclusions submitted. Such disregard of important component factors is entirely at variance with the analytical and mathematical rules for the treatment of problems and equations containing several variables.

It is also quite against these rules not carefully to analyze the formulas and mathematical conceptions employed. Such formulas and conceptions cannot be properly utilized unless their implications and bearings are distinctly understood; it is also a very primitive and little informative method to employ formulas merely for more or less mechanical computation of quantities, as is so often the case in present renal physiology. Formulas and quantitative conceptions should be analyzed in the first place; their application to particular instances of computation is a very secondary matter, and the results of such computations cannot even be used for testing the validity of the formulas unless the bearings and implications of these have first been worked out and duly considered.

My earlier papers in this series:

- I. Inuline as a substitute for creatinine in renal tests. This journal, vol. 118, p. 114—62.
- II. The importance of adequately recorded results in Rehberg's kidney test. Ibid. vol. 119, p. 57—102.
- III. The normal excretion of urinary constituents of low tubular re-sorbability, together with remarks concerning the variability of glomerular filtration. Ibid. vol. 120, p. 227—258.

(From the Physiological Department, Karolinska Institutet, and the Medical Physiology Laboratory, Medical Department, Karolinska Sjukhuset, Stockholm.)

## Pressor activity in urine in hypertension.

By

U. S. v. EULER and T. SJÖSTRAND.

(Submitted for publication November 21, 1944).

---

It has been frequently assumed that humoral factors are, at least partly, responsible for the development of hypertension, either through the mediation of pressor substances or through a deficit of depressor substances. Numerous investigations on the occurrence and amount of blood pressure active substances in blood and urine have been undertaken, though the results have not been unanimous. In a previous paper we have reported some experiments on the occurrence of pressor substances in blood and plasma from healthy persons and from patients with hypertension. The results were negative in so far as the blood of the hypertensives did *not* contain more dialysable pressor activity than the normal blood or plasma with the methods used. In fact there was — on an average — less pressor action in the blood of the hypertensives (mostly essential hypertension) than in normal blood.

It seemed of interest to extend this study also to urine, since a concentration of active substances in urine would be conceivable, and such substances probably easier to prepare and investigate.

Several authors have reported the occurrence of blood pressure active substances in urine. Abelous and Bardier (1908) found an ether-soluble pressor substance which was rather active on the blood pressure of the dog. After the isolation of *iso*-amylamine from organic material by Barger and Walpole (1909), Bain undertook

to study the chemical nature of a pressor constituent of normal urine, obtained by adsorption on charcoal, assuming it to be identical with Abelous and Bardier's «urohypertensin». He arrived at the conclusion that it was *iso*-amylanine. He also obtained certain evidence of the occurrence of a second pressor substance. Abelous and Bardier and Bain noted that the pressor activity was greater in normal urine than in urine from hypertensives and patients with arteriosclerosis.

Bohn and Hahn (1933) obtained a stronger pressor action with alcoholic extracts of adsorbates on silica gel from urine in pale hypertension than from normal urine or from red hypertension. Page (1934) found that a great part of the pressor action of fresh urine could be extracted with ethyl acetate. No difference was found between the amount of pressor substance in urine from normal persons and hypertensives. On the other hand Capps, Ferris, Taylor and Weiss (1935), using Bohns method, found on the whole more marked pressor responses with extracts of urines from normal subjects than from patients with hypertension (malignant and nephritic hypertension). Similar results were obtained by Euler and Sjöstrand (1943) who used ethereal extracts of urine. It has been pointed out by Helmer, Kohlstaedt and Page (1939), however, that nicotine in smokers' urine may be responsible for the stronger pressor action found in urine from normals than in hypertensives since the latter presumably use less tobacco.

Recently Enger et al. (1944) has reported that urine from dogs with experimental renal hypertension contains nephrin, a pressor principle previously found in the blood of hypertensive patients.

In the present paper an account will be given of experiments with extracts from urine of normals and hypertensives and their pressor action compared on the blood pressure of the cat.

### *Methods.*

Urine was collected from patients with hypertension and various diseases and also from normal persons which were known to be non-smokers. Unless otherwise stated, the urine was collected for 24 hour periods. Care was taken to keep the urine cold during the collection period. In order to prevent bacterial growth a small quantity of toluol was added to the urine. A known amount of the

urine was concentrated in vacuo to about  $\frac{1}{5}$  of its volume at a slightly acid reaction. The concentrated urine was made alkaline with NaOH, extracted with 2—3 volumes of alcohol and filtered after standing in the refrigerator for 12—24 hours. The alcohol was removed from the acidified filtrate by distillation in vacuo.

Alcoholic extracts of urine seemed to contain practically all of the pressor activity, leaving certain depressor constituents such as kallikrein (Frey and Kraut, 1928) and depressan (Wollheim, 1937) behind. Though the urea, present in large quantities in alcoholic extracts of urine, did not seem to exert any marked effects when moderate amounts of urine were tested, it in larger amounts tended to interfere with the action of pressor substances. It therefore became necessary to remove the urea which was firstly tried with urease. This method did not seem to be satisfactory for routine work and we therefore tested whether the pressor activity could be extracted with ether. This proved to be the case and the method of fluid extraction with ether was adopted. A comparison between the original extract, the ether extract and the residue after ether extraction showed that practically all of the pressor activity could be extracted with ether at alkaline reaction. For a complete extraction — or as nearly complete as was desirable in our experiments — extraction was continued for 3—6 hours depending on the intensity of extraction at a reaction of pH 10—11. To the ether extract was added 5—10 ml water and 2 N sulphuric acid sufficient to extract water soluble bases from the ether. The water phase was separated from the ether and, after removal of the ether, tested on the blood pressure of the cat in chloralose anaesthesia. In a few cases where extraction with ether at acid reaction (pH 4) was tried, some pressor activity was observed, though this was rather weak. Possibly this activity corresponds to the nephrin of Enger, which is reported to be soluble in ether at acid but not at alkaline reaction.

### *Results.*

#### *a) Pressor activity in normal urine.*

Ethereal extracts from normal urine, containing the active bases as sulphates, regularly caused a pressor effect on the cat's blood pressure. The pressor responses were in the beginning registered

Table 1.  
*Pressor activity of urine from healthy non-smokers.*

Nr.	Sex	Age	Activity of 100 ml urine in terms of mg <i>iso-amyl-amine-HCl</i>	Total activity per 24 hours
N 89	O	2	0.5	5
IR 1	O	20	2.5	25
IR 2	O	20	2.5	25
IR 3	O	20	1	8
IR 4	O	20	2.5	20
N 103	O	6	3	21
N 104	O	6	2	10
N 92	O	10	3	13
N 93	O	12	3	18
IR 1a	O	24	0.5	6
IR 2a	O	22	0.3	3
IR 3a	O		1	10
IR 4a	O	20	4	40
N 116	O	23	0.5	10
N 117	O	22	1.5	21
N 118	O	23	2	17
N 119	O	22	1.5	20
N 120	O	21	3	58
N 120a		21	2	40
N 120b		21	3	48
N 121	O	24	2.5	16
N 122	O	23	1.5	19
N 123	O	21	4	40
N 123a		21	2	24
N 123b		21	2.5	29
N 123c		21	2	24
N 123d	O	21	3	36
N 124		22	2	26
N 125	O	24 = N121	2	31
N 125a		24	3	42
N 125b		24	2	28
N 125c		24	2	36
N 126	O	21	1.5	19
N 127	O	22	2	30
N 128	O	21	1.5	22
N 129a	O	20	1.5	15
N 129b		20	1	13
N 129c		20	1.5	11
N 129d		20	1.5	15

semi-quantitatively as +, ++, +++ and +++++, but since the sensitivity of the animals varied considerably, *iso*-amylamine hydrochloride was later used as a standard substance in order to obtain a better quantitative measurement.

The observations of Helmer, Kohlstaedt and Page that nicotine may interfere with the evaluation of pressor activity of urine could be confirmed. It was therefore necessary to select the cases carefully with regard to the use of tobacco.

The amount of extract injected corresponded to 100 ml fresh urine. As a rule the pressor effect was clean, but in a few cases a slight depressor effect preceded the rise. The type of pressor action showed certain variations in different cases.

In the opposite table the effects have been given in terms of *iso*-amylamine hydrochloride as a standard, though certain observations have led us to doubt that this substance is wholly responsible for the effect.

From the table it is evident that all urines from healthy non-smokers, irrespective of sex, contain ether soluble pressor substances to a considerable degree. This is in agreement with the results obtained by Abelous and Bardier and Bain. There are certain variations in the amount, however, the reason for which can not be given at present. It is obvious, on the other hand, that the urine taken from the same persons in a series of consecutive days seem to have about the same activity. Thus the figures for N 120, N 123, N 125 and N 129 agree fairly well in each case, though the 3 first ones show definitely higher figures than N 129. It should be noted that in those four cases where figures lower than 10 were obtained, we have found no signs of abnormal conditions. The average activity of the 24 hour urine extracts expressed in the units chosen is  $23 \pm 2$ . With regards to age we have not found any consistent dissimilarities between various extracts.

As to the nature of the pressor substance it seems to agree superficially with the substance of Bain in its action and other properties. The observation by Tainter (1933), that the action of *iso*-amylamine is abolished by cocaine in a dose of 10 mg per kg made it desirable, however, to test the action of our extracts in this respect. In a few cases the pressor effect was diminished or even suppressed by cocaine though in most cases the effect was unchanged or even reinforced. In the former case it seems

Table 2.

*Pressor activity of urine from normotensive patients.*

Number	Age	Blood pressure	Total activity in 24 hour samples (in mg iso-amylamine-HCl)	Clinical diagnosis
N 8	56	140/75	17	Gastro-duodenitis chron.
H 18	46	145/90	22	Varic. erur. + arthr. def.
N 9	74	120/70	24	Polyarthr. + cardioscl.
N 10	60	115/75	12	Periarthr. calc. genu dx.
H 19	40	150/85	18	Haemoptys. inc. caus.
H 21	35	105/55	9	Vitium org. cord.
N 12	57	130/75	20	Hernia diaphragm.
N 13	55	110/75	21	Ulcus duod.
N 16	43	115/80	25	Polyarthr.
N 18	53	140/70	28	Polyarthr.
H 24	59	150/80	12	Incompens. cord.
N 19	69	135/80	12	Ulcus vent.
N 22	42	115/75	18	Endocrinol. disturb.
N 26	33	130/75	18	Tbc. pulm.
N 40	30	115/70	8	Colitis ulc.
N 41	40	105/70	8	Tbc. spondyl.
N 42	51	140/70	22	Hyperthyreosis.
N 43	37	135/85	11	Enterocolitis
N 44	36	130/85	20	Vitium org. cord.
N 45	45	125/65	26	Lues + polyarthr.
H 39	54	125/65	0	Diabetes mell. + polyarthr.
N 54	45	140/70	7	Ulcus duod.
N 56	48	145/70	14	Colit. ulc.
N 57	51	145/75	21	Febris rheumatica.
N 61	42	110/75	24	Polyarthr. chron.
N 69	54	160/95	38	Polyarthr. chron.
N 71	38	120/80	55	Anaemia perniciosa
N 72	64	145/70	14	Cancer
N 77	48	130/80	30	Polyarthrititis
N 90	32	135/90	20	Polyarthrititis
N 95	34	135/75	32	Vit. org. cord. incomp.
N 131	53	135/80	16	Polyarthr. chron.
N 132	40	145/100	10	Polyarthr. subac.
N 135	37	125/80	20	Sclerosis diss.
N 136	43	135/85	0	Polyarthr. chron.
N 138	60	110/80	10	Polyarthr. chron.
N 139	52	135/100	24	Neurosis vegetativa
N 140	31	normal	20	Lymphadenitis
N 141	50	100/60	20	Nephrolith.
N 142	54	110/80	21	Pancreatitis chron.



(Tab. 2. contin.)

Number	Age	Blood pressure	Total activity in 24 hour samples (in mg iso-amylamine-HCl)	Clinical diagnosis
N 145	54	155/100	24	Cholelith.
N 147	32	95/55	13	Tbc. pulm.
N 149	49	150/80	12	Polyarthr. chron.
N 150	54	155/100	20	Cholelith.
N 152	51	135/70	12	Hypothyrcos.
N 153	47	150/100	5	Polyarthr. chron.
N 154	44	140/95	8	Obesitas
N 155	46	135/75	14	Hypothyrcos.
N 158	50	160/110	13	Obesitas
N 159	37	125/80	9	Pleur. exsud.
N 163	68	150/70	10	Ulcus ventr.
N 167	56	125/90	6	Myocard. chron.
N 171	72	140/70	5	Polyarthr.
N 172	48	140/60	9	Achylia gastr.
H 32	30	100/70	25	Hypert.malign.sympathect.
H 35	37	130/80	24	Hypert. ess. sympathect.
H 45	52	155/100	24	Hypert. ess. sympathect.
H 42 a	34	140/100	12	Hypert. ess. sympathect.
H 54 a	34	130/90	30	Hypert. ess. sympathect.

reasonable to assume that the action has been partly or chiefly due to iso-amylamine, which is affected in the same way (fig. 1). In the majority of cases, however, where the effect was uninfluenced by cocaine, it is obvious that some other substance must have been the cause of the effect. We have not investigated this substance further, though it does not seem improbable that it is identical with a pressor substance isolated from cow's urine and which has subsequently been shown to be piperidine (Euler, 1944).<sup>1</sup>

*b) Pressor effects of extracts of urine of patients with normal blood pressure.*

In order to obtain a material which could be more directly compared with the hypertensive in-door patients we have tested urine extracts from a number of patients with various diseases. Only female patients have been selected in view of the difficulties

<sup>1</sup> Added in proof: Piperidine has since been prepared from human urine and accounts for the chief part of its pressor action. (Acta pharm. scand. 1945, I, in press).

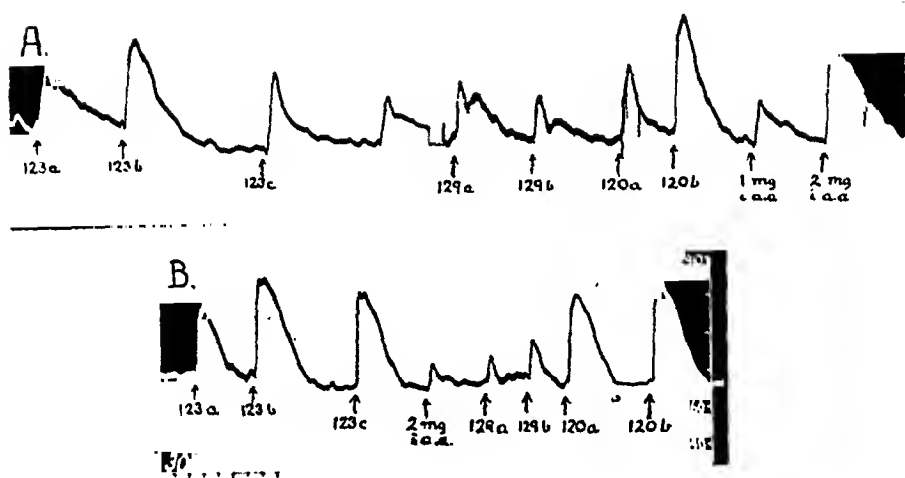


Fig. 1. Cat, chloralose, blood pressure. 0.05 mg ergotamine tartrate per kg i.v. A before and B after 5 mg cocaine hydrochloride per kg intramuscularly. Figures mark injection of extract of 100 ml urine from 3 healthy persons; a, b, c, indicate samples from different days. i. a. a. = isoamylamine hydrochloride.

of excluding the use of tobacco. The foregoing Table 2 contains the relevant data from this material.

In this material all cases of less than thirty years of age have been excluded in order to bring the average age up to a figure corresponding to that in the hypertensive material which is presented in Table 3. Thus the average age in the 59 cases reported here was 47 years. It should be noted, however, that this limiting of the material has affected the results only to a minor degree. The average total activity of the extracts in Table 2 is  $17.0 \pm 1.2$ , and that of the 15 patients less than 30 years was  $15.9 \pm 2.1$ .

From the figures in the Table 2 it seems that urine from female patients without hypertension contained on an average about the same pressure activity as normal healthy persons (see Table 1). Several factors may contribute to the fairly large variations between the individual figures. On the whole the medical treatment does not seem to cause any greater effects. Certain drugs, however, such as ephedrine, are recovered in our extracts and may cause profound pressor effects. Also coffee may interfere with the results of the biological testing. Those cases where obvious side-effects have been observed were excluded from the material. A subdivision of the material with respect to the different diseases

Table 3.

*Pressor activity of urine from hypertensive patients.*

Number	Age	Blood pressure	Total activity in 24 hour (in mg iso-amylamine-HCl)	Clinical diagnosis
H 3	31	220/140	0	Nephrit.chron.
H 4	65	230/130	0	Hypert. + arterioscl.eer.
H 7	65	200	7	Hypert. + arterioscl.eer.
H 9	31	220/140	0	Nephrit.chron.
H 12	61	245/115	18	Hypert. + Cardioscl.
N 7	56	220/120	8	Hypert.ess.
H 17	51	280/135	7	Hypert.ess.
N 17	57	220/120	4	Hypert.ess.
H 22	59	200/100	6	Hypert.ess.
H 23	62	180/90	5	Hypert.ess. + polyarthr.chron.
H 26	44	210/120	11	Hypert.ess.
H 27	78	170/90	3	Hypert.ess. + polyarthr.chron.
H 28	52	215/100	11	Hypert.ess.
H 29	18	175/100	4	Hypert.ess.
H 30	56	180/95	9	Hypert.ess.
H 33	38	255/145	10	Hypert.ess.
H 36 (=H 17)	57	280/135	0	Hypert.ess.
N 51	54	185/100	4	Hypert.ess. + polyarthr.chron.
H 38	52	190	6	Hypert.ess.
H 41	—	200/90	10	Hypert.ess. + cardioart.scl.
N 60	40	225/120	0	Nephrl.chron.
N 78	53	250/140	6	Hypert.ess.
H 43	39	180/110	3	Hypert.ess.
H 46	39	210/115	0	Hypert.ess.
H 47	53	220/105	18	Hypert.ess.
H 48 (=H 17)	52	200	0	Hypert.ess.
H 49	37	250/170	30	Hypert.ess.
H 55	55	230/120	12	Hypert.ess.
H 57	40	200/110	33	Hypert.ess.
H 61	53	200	10	Hypert.ess.
H 65	51	200	10	Hypert.ess.
H 66	—	245/160	10	Hypert.ess.
N 130	58	210/125	20	Hypert.ess.
N 133	62	185/100	40	Hypert.ess. + spond.def.
N 146	54	200/120	11	Hypert.ess.
N 168	44	170/110	0	Hypert.ess. + cirrh.hep.
N 175	53	195/120	4	Hypert.ess.

would seem hazardous at present. We have the impression, however, that cases of polyarthrititis in the acute stages show higher figures than the rest. On the other hand some of the lowest figures belong to cases with chronic polyarthrititis. In the cases of hypertension successfully treated with partial sympathectomy the average figure was 23.

a) *Pressor effects of extracts of urine from patients with hypertension.*

In the following material, comprising 37 cases, all female, most of the patients suffered from hypertension of the essential type. Table 3 gives the data from these patients.

The average age of the hypertensive material in Table 3 was 51 years and the potency of the extracts is  $8.9 \pm 1.5$  in terms of mg iso-amylamine hydrochloride per 24 hours. For the cases with pure essential hypertension the average was 9.7.

A comparison between this material and the non-hypertensive material gives a difference of  $8.4 \pm 1.9$  which is statistically significant.

The results are that urine from clinical cases of essential hypertension does not contain more ether soluble pressor substances than urine from comparable clinical cases with various diseases chosen at random. There is, on the contrary, in our material a statistically lower content of pressor activity in urine from patients with hypertension. It should also be noted that in the three cases of chronic nephritis the amount of pressor substances was so low that it could not be determined with certainty.

### Discussion.

It seems difficult at present to correlate these findings with other facts pertaining to the state of hypertension of the essential type. In the work of Capps et al. the results seem to be of a similar kind — if a nicotine effect can be excluded — whereas no such difference was observed in the experiments quoted by Page. At any rate it may be considered as established that urine from hypertensive patients does not contain more pressor activity than urine from normotensives, but actually, as in our material, may contain less.

It is of interest to note that a similar difference between normotensives and hypertensives applies to the pressor activity of blood and plasma (Euler and Sjöstrand, 1944). In this connection it should also be recalled that Major (1928) has observed a reduced ability in hypertensive patients to excrete creatinine and certain guanidine derivatives. Also with regard to the excretion of depressoan, an undialysable substance in urine, Wollheim states that hypertensive patients secrete less than normotensives. Whether the reduced secretion of these rather dissimilar substances can be brought back to a general disturbance of a uniform kind cannot as yet be ascertained. Since there is little reason to assume a lowered secretion from the kidneys it appears as most probable that some metabolic change is the cause of the difference observed between normotensives and hypertensive patients.

### Summary.

Ether extracts of urine from healthy persons and patients with various diseases including hypertension have been prepared and tested with regard to their activity.

The presence of pressor substances in urine from healthy persons has been confirmed.

The pressor activity of urine from patients with various diseases but with normal blood pressure did not differ significantly from that of healthy persons.

In 37 cases of hypertension the pressor activity was significantly less.

The pressor action does only partly agree with that of isomylamine which has generally been assumed to account for the pressor action of urine.

The costs of this investigation have been defrayed by grants from the Therese and Johan Andersson Memorial Foundation and from Astra Ltd., Södertälje. We also wish to acknowledge the valuable technical assistance of mr E. Östlund throughout this work.

## References.

- Abelous, J. E. and E. Bardier: *J. physiol. Pathol. Gén.*, 1908, *10*, 627. — Bain, W.: *Quart. J. exp. Physiol.*, 1914, *8*, 229. — Barger, G. and G. S. Walpole: *J. Physiol.*, 1909, *38*, 343. — Bohn, H. and F. Hahn: *Z. Klin. Med.*, 1933, *123*, 558. — Capps, R. B., E. B. Ferris, F. H. Taylor and S. Weiss: *Arch. int. med.*, 1935, *56*, 864. — Enger, R. and I. Kulczycky-Polivka: *Z. Klin. Med.*, 1944, *143*, 410. — Euler, U. S. v.: *Nature*, 1944, *154*, 17. — Euler, U. S. v. and T. Sjöstrand: *Nature*, 1943, *151*, 168. — Euler, U. S. v. and T. Sjöstrand, *Acta med. Scand.*, 1944. — Frey, E. K. and H. Kraut: *Arch. exp. Pathl. & Pharm.*, 1928, *133*, 1. — Helmer, O. M., K. G. Kohlstaedt and I. H. Page: *Amer. Heart. J.*, 1939, *17*, 15. — Major, R. H.: *Am. J. med. Sci.*, 1928, *176*, 637. — Page, I. H.: *Proc. Soc. exp. biol. Med.*, 1934/35, *32*, 302. — Tainter, M. L.: *Arch. inst. Pharm. Thér.*, 1933, *46*, 192. — Wollheim, E.: *Acta med. Scand.*, 1937, *91*, 1.
-

From the Medical Clinic of the Serafimer Hospital, Stockholm.  
Head Physician: Prof. A. Kristenson.

## The Ulcer and Wartime.

A study of the Serafimer Hospital's ulcer cases in recent years.

By

THOR SÄLLSTRÖM M. D.

(Submitted for publication November 3, 1944).

---

In the course of my duties at the Serafimer Hospital's Medical Clinic, I have during the last few war years (1939—42) formed the impression that cases of gastric ulcer and duodenal ulcer have become more numerous and that the results of treatment have become worse than during the years immediately prior to the war. The effects of wartime conditions on ulcerous diseases have in various ways been the subject of discussion during recent years, and in a paper a short time ago Malmros and Björhn declared that they had observed a deterioration of the healing tendency in cases of stomach ulcers during the years 1942. The question is therefore an urgent one, and every investigation that can in any way shed light on these circumstances should therefore be of interest.

Between the years 1930 and 1942, 2,449 ulcer cases were diagnosed by means of X-rays at the Serafimer Hospital's Medical Policlinic. These cases consisted of patients from both town and country, but mainly from the towns. Of these 2,449 ulcer cases, 608 were cases of gastric ulcers and 1,841 cases of duodenal ulcers, i.e. about 25 % gastric ulcers and 75 % duodenal ulcers (see Table 1). On the whole an increase has taken place in the number of ulcer cases during these years, but there has not been any steady rise. The figure has merely varied somewhat from year to year, sometimes up and sometimes down. Not until 1942 is there an appre-

ciable increase in the number of cases, which reach a figure corresponding to approximately one ulcer case per day. There are many different factors which might possibly influence the increase in the number of ulcer cases encountered at the Polyclinic. The increase observed here may for the most part be explained by a growing tendency to X-ray patients with suspected stomach-trouble histories. During recent years stomach cases have been almost invariably X-rayed, but this used not to be the case. If one studies the annual reports of the Medical Polyclinic for the corresponding years, it will be found that the figures for ulcer cases, which at the beginning of the period vary quite considerably (during the first few years 3 or 4 times as many in the annual reports as those given in my table), gradually show increasingly close agreement, and during the last few years deviate only slightly from one another. It is not possible therefore to show any definite absolute increase in the incidence of ulcer cases. The increase in these clinical cases referred to is mainly due to improved diagnosis as a result of the X-ray examination of stomach cases. Owing to this and also to a

Table 1.

The table shows ulcer cases *diagnosed by X-rays* at the Serafimer Hospital's Medical Polyclinic over the period 1930—1942.

Year	No. of ulcer cases		Total	% duodenal ulcers	Gastric ulcers			Duodenal ulcers		
	gastric	duodenal			♂	♀	% ♂	♂	♀	% ♂
1930	27	75	102	72	18	9	66	56	19	74
1931	19	121	140	86	12	7	63	97	24	80
1932	32	75	107	71	21	11	66	53	22	71
1933	21	132	153	84	15	6	71	92	40	70
1934	55	143	198	74	34	21	61	109	34	76
1935	44	93	137	68	32	12	72	68	25	73
1936	50	161	211	78	34	16	68	118	43	73
1937	69	197	266	74	40	29	58	144	53	73
1938	39	139	178	78	23	16	59	94	45	67
1939	39	174	213	82	24	15	61	127	47	73
1940	61	171	232	74	41	20	67	126	45	74
1941	54	130	184	71	38	16	70	102	28	77
1942	98	230	328	71	65	33	66	157	73	69
	608	1841	2449	75	397	211	65	1343	498	73



number of other circumstances the ulcer cases at the Serafimer Hospital's Medical Policlinic are probably not quite suitable for the purpose of deciding whether an increase in the incidence of ulcer illnesses has taken place during the period under review.

The ulcer cases comprise 25 % gastric ulcers and 75% duodenal ulcers. These percentages differ to a certain extent for the various years, but the variations are so slight as to be of no importance. There is a definite preponderance of duodenal ulcers and most authors of literature on the subject indicate that there have been proportionately more cases of duodenal ulcers than of gastric ulcers in recent years. (von Bergmann, Kalk, Nicol and Weidinger). Only a few of them, including Madelung claim that gastric sores are more usual than duodenal sores.

The 2.449 ulcer cases are apportioned between the sexes in the following manner: 1.740 men and 709 women. The proportions between men and women are somewhat different for the two forms of ulcer. On the average, 65 % of the gastric ulcer cases and 73 % of the duodenal ulcer cases are men. The departures from these average figures for the years in question are quite insignificant. No change in the proportions between men and women during the period under review, 1930—1942, has taken place. In a series of cases from the Serafimer Hospital covering the years 1914—1934 Holmgren has shown that such a change actually did take place, the number of male cases increasing and the number of female cases declining. Hansen states the same. Most authors give figures which tally very closely with mine (Alsted, Hansen, Nicol, Weidinger, Wiebel and Kunstréich).

From this body of ulcer material I have mostly studied the ulcer cases which have been received and treated by the Hospital's Medical Clinic from the years 1937—1942. I have divided this period up into two sections, the first covering the years from 1937—1939 and corresponding to peacetime conditions and the second section covering the war years 1940—1942. These sections have then been compared with each other from various aspects.

The number of ulcer cases throughout the whole period 1937—1942 is 656, 261 cases of gastric ulcers and 395 cases of duodenal ulcers. Table 2 gives the figures for these cases, and it can be seen from this table that the apportionment of ulcer cases as between men and women accords with the figures given by me above.

It is interesting to note that the number of ulcer cases treated every year at the Clinic shows a considerable increase during the period 1940—1942. Thus in the year 1942 more than twice as many cases of ulcers were treated as in earlier years. As observed above, it cannot be stated, with any certainty that the number of ulcer illnesses has increased during the period under review, but it can be seen that the number of ulcer cases that have been subjected to treatment has increased. Therefore the fact that the number of ulcer cases treated at the Clinic has increased, while no certain increase in the incidence of the illness has occurred, must be due to external circumstances. For the most part it can probably be attributed to the increased difficulty of providing dietary food at home.

Another interesting feature of this table is the ratio of gastric ulcer cases to those of duodenal ulcers. Among the cases treated there may be found here a ratio between the two ulcer types of 40: 60 (for both periods alike). As I indicated above, the corresponding figure for all the ulcer cases at the Medical Clinic is 25: 75. Here therefore we find a difference, and it is so great as to be a statistical certainty. Thus a proportionally greater number of gastric ulcer cases than duodenal ulcer cases are treated at the Hospital. I have been unable to find any explanation for this.

Table 2.

Ulcer cases treated at the Medical Clinic between 1937 and 1942.

Year	Gastric ulcers			Duodenal ulcers			Total	% Duodenal ulcers
	♂	♀	♂+♀	♂	♀	♂+♀		
1937	22	10	32	37	14	51	83	61
1938	16	9	25	29	12	41	66	62
1939	13	8	21	31	6	37	58	63
	51	27	78	97	32	129	207	62
	65%	35%		75%	25%			
1940	30	14	44	38	27	65	109	60
1941	46	17	63	62	17	79	142	57
1942	52	24	76	84	38	122	198	62
	128	55	183	184	82	266	449	60
	70%	30%		69%	31%			

I have also studied the age groups of the Clinic's cases. As regards the age of ulcer patients, it is of course not the age at the time of diagnosing the illness that is of primary interest but the age at the start of the illness. In the histories of ulcer patients one finds most frequently that the patients have periodically had stomach trouble for several years. One has therefore to determine with the aid of the past history of the case, at what age the patient experienced stomach trouble for the first time. It is obvious that this procedure leads to relatively uncertain results, but the age arrived at in this way must, at any rate in relation to the age at the time of treatment, be reduced in the right direction and correspond more or less to the actual age. The figures showing the ages at which stomach trouble was first experienced are given in Table 3.

One interesting aspect of the division into age groups in this connection is the question whether any difference is discernible between the pre-war period and wartime. The figures for the two periods 1937—39 and 1940—42 correspond fairly well, especially as regards cases of duodenal ulcers. As far as cases of gastric are concerned, a somewhat higher incidence in the 26—45 age group

Table 3.

Distribution of ulcer cases among the various age groups.

Age Group	Gastric ulcers		Duodenal ulcers		Total ulcers		Population in towns in various age groups $\times 1000$ (a)	Gastric ulcers in % of (a)	Duodenal ulcers in % of (a)
	1937—39	1940—42	1937—39	1940—42	gastric	duodenal			
16—20	9	14	21	48	23	69	156	0.14	0.44
21—25	10	15	28	42	25	70	167	0.15	0.42
26—30	7	20	26	41	27	67	159	0.17	0.42
31—35	10	26	17	38	37	55	148	0.25	0.37
36—40	6	27	10	28	33	38	131	0.25	0.29
41—45	10	23	10	22	33	32	115	0.29	0.28
46—50	8	13	7	11	21	18	93	0.23	0.20
51—55	5	16	5	13	21	18	78	0.26	0.23
56—60	8	12	4	8	20	12	74	0.27	0.16
61—65	3	13	4	6	16	10	62	0.25	0.16
66—70	2	5	1	8	7	9	45	0.15	0.16

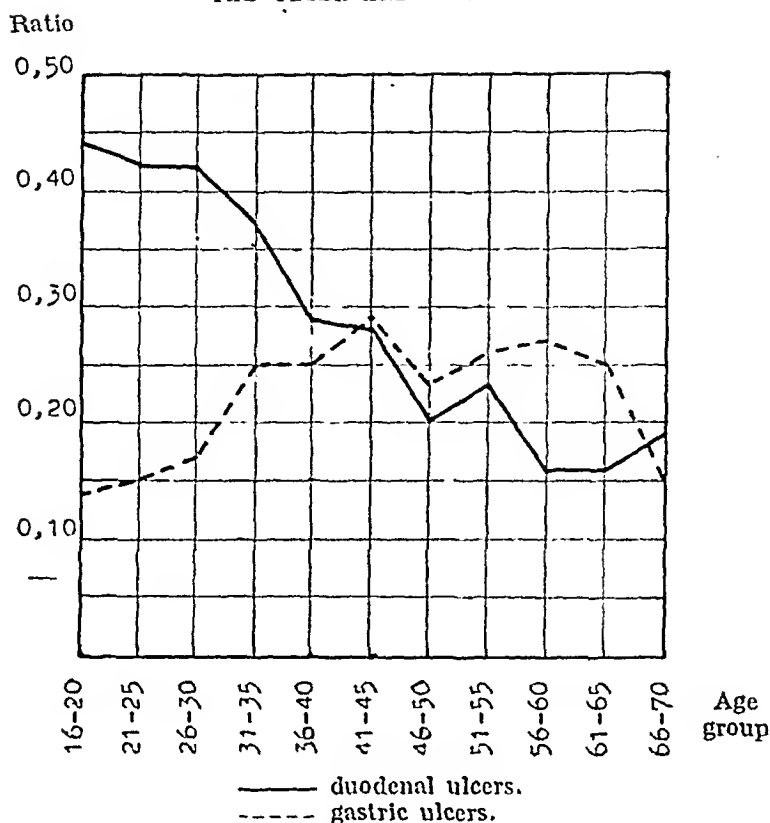


Figure 1.

for the period 1940—42 can be observed. The variation is, however, too slight to merit further mention.

The distribution among the various age groups is of course in itself interesting. Figure 1 shows the ratios obtained by correlating the ages with the number of persons in the population within the corresponding age groups. Here it is clearly seen that duodenal ulcers are commonest in the younger age groups, i.e. between 16 and 40, while the gastric ulcer curve steadily rises until it attains its peak at the 41—45 age group, after which it slowly falls again. That no cases under the age of 16 are included is due to the fact that young patients are only admitted to the Serafimer Hospital in exceptional cases. The incidence of ulcer cases under the age of 16 cannot therefore be studied here. To sum up, then, it can be said that there is a clear differentiation between the age distribution among patients belonging to the gastric ulcer group and those belonging to the duodenal ulcer group, a fact which was observed earlier by, among others, Nicol, Kalk, Weidinger, Wiebel and Kunstreich.

In this review I have dwelt at some length on the composition of the material and have also to some extent compared its structure with ulcer material dealt with in previous literature on the subject. Familiarity with the material is in the first place of great interest and in the second place of importance for the consideration of the remainder of the investigation. How far is it possible with the aid of this material to determine whether any deterioration in the effects of treating ulcers with the ulcer cure can be traced in recent war years? A comparison of ulcer treatment for the two periods 1937—39 and 1940—42 shows that it has changed appreciably in only one respect, viz. diet. The factors which, having regard to these circumstances, might possibly be able to illustrate the results of ulcer treatment are in the main following:— 1) the duration of the treatment, 2) the time taken for the sore to heal, 3) weight before and after the cure, 4) the type of evacuation of the bowels, and 5) the tendency to a relapse.

As to the duration of treatment, an appreciable difference, between the two periods is discernible. During the period 1940—42 the duration of treatment for ulcer cases is considerably longer than for the earlier period. Table 4 shows the respective figures and Figure 2 displays the conditions in the form of a graph. For the first group, 1937—39, the duration of treatment is in more than 60 % of the cases no longer than 4 weeks, while for the period 1940—42 the time of treatment is only in 30 % of the cases completed within the same period of time. What is the implication of the fact that the time of treatment has been so very much longer in recent years? The post of chief medical officer at the Serafiner Hospital's Medical Clinic has changed hands several times during the period covered by the investigation, but there has been a regular chief medical officer since 1941. It is possible that since 1941

Table 4.

The duration of treatment in weeks for the periods under review 1937—39 and 1940—42.

Period	Number of cases	Duration of treatment in weeks											
		1	2	3	4	5	6	7	8	9	10	11	12
1937—39	206	15	19	20	75	38	14	9	11	2	2	0	1
1940—42	453	25	12	31	78	106	97	51	31	10	3	5	4

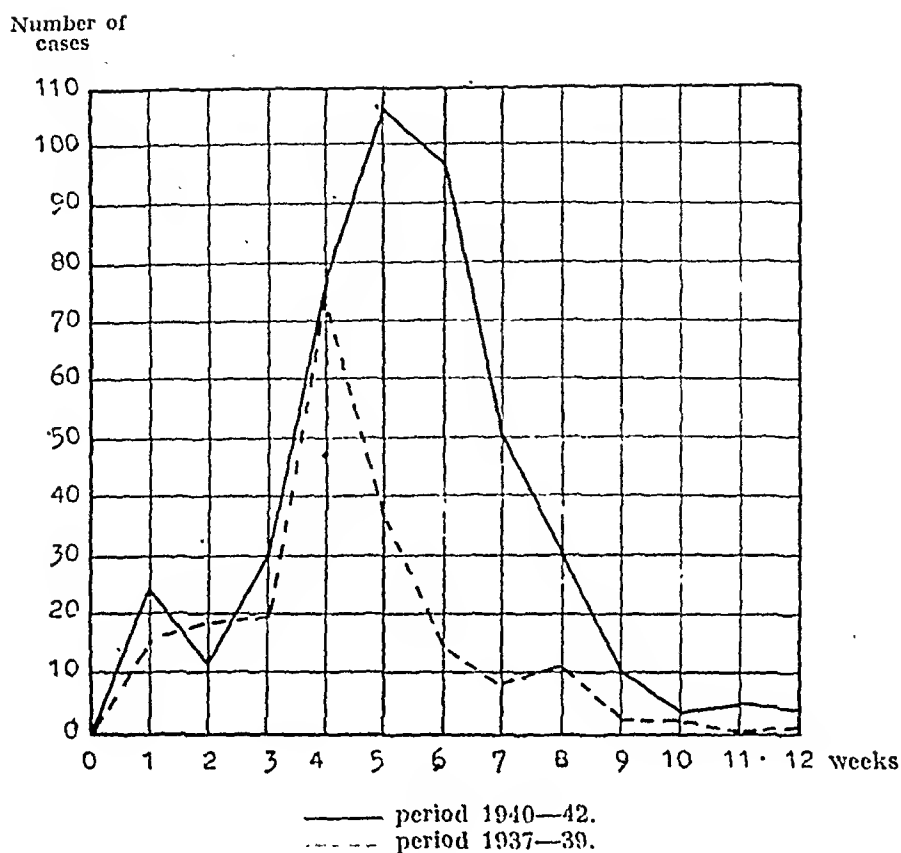


Figure 2.

Duration of treatment in weeks for the periods 1937—39 and 1940—42.

the duration of treatment has as a matter of principle been somewhat longer than previously. The prolonged duration of treatment for ulcer patients during the period 1940—42 may however also be due to a slower healing of the sores.

Exactly what is meant by the healing of a gastric ulcer or a duodenal ulcer is of course open to discussion. Here I have employed the expression «the healing of the sores» to signify the stage when upon X-ray examination after the completion of the ulcer cure they no longer exhibit niches. Thus, healed cases are taken to include those cases where the healing has proceeded in conjunction with the deformation of the bulb. It is obvious that X-ray examination is not conclusive when it comes to determining changes in ulcers, but on the whole it is probably the only objective method existing for determining cases. As a rule the first X-ray examination

Table 5.

Cases which by means of X-ray control proved to have healed (BD = bulb deformation).

Year	No. of cases	No control	X-ray controlled	No. of cases healed	No. of cases healed		Percentage of healed cases
					with BD.	without BD.	
1937	83	31	52	30	11	19	57
1938	66	18	48	28	13	15	60
1939	58	11	47	34	16	18	72
	207	60	147	92	40	52	63
1940	109	23	86	57	33	24	66
1941	142	11	131	89	42	47	68
1942	198	30	168	96	55	41	57
	449	64	385	242	130	112	63

of ulcer cases is carried out when the ulcer cure has been applied for 3 or 4 weeks. If further control has proved necessary, it has been carried out about 14 days later. This, on the whole, has been the principle followed during the entire period under review.

If therefore one bears in mind the above definition of healed ulcers, one find that the percentage of healed sores is approximately the same for both periods (Table 5). In both groups about 63 % of the cases are discharged as cured. *Thus the ulcer cure, whether of long or short duration, gradually results in the same number of healed cases for both periods.*

It is very interesting, moreover, to study the cases that have not healed. Table 6 shows the figures and Table 7 shows the percentage of cases remaining unhealed after 4, 5 and 6 weeks respectively, compared with the total number of unhealed cases in the two periods. After 4 weeks about 85 % of the cases still remain unhealed in both the periods; after 5 weeks about 45 % still remain unhealed in the 1940—42 group, while only 28 % in the 1937—39 group have failed to heal. Finally, after 6 weeks 28 % of the cases remain unhealed in the first group but only 18 % in the second group. This indicates that *the healing of ulcers has taken place more slowly during the later period — in wartime —.* Thus the cure

Table 6.

Cases where X-ray examination has shown the continued presence of an ulcer.  
GU = gastric ulcer, DU = duodenal ulcer.

Year	Number of cases remaining unhealed after																	
	2 weeks		3 weeks		4 weeks		5 weeks		6 weeks		7 weeks		8 weeks		9 weeks		Total	
	g.u.	d.u.	g.u.	d.u.	g.u.	d.u.	g.u.	d.u.	g.u.	d.u.	g.u.	d.u.	g.u.	d.u.	g.u.	d.u.	g.u.	d.u.
1937	0	0	2	3	5	8	0	0	1	1	2	1	1	0	0	0	11	13
1938	0	0	1	1	4	6	0	5	1	2	0	0	0	0	0	0	6	14
1939	0	0	1	3	3	9	1	0	0	1	0	1	1	0	0	0	6	14
	0	0	4	7	12	23	1	5	2	4	2	2	2	0	0	0	23	41
1940	0	2	2	5	14	12	1	0	3	1	2	1	0	1	2	1	24	23
1941	0	0	5	2	10	7	10	3	4	6	3	3	0	0	0	0	32	21
1942	1	4	4	1	9	21	6	9	6	8	1	4	2	0	3	0	32	47
	1	6	11	8	33	40	17	12	13	15	6	8	2	1	5	1	88	91

must be carried on longer before the same effect is obtained as in the earlier period.

The patient's weight, i.e. the difference in weight on admittance to hospital and on discharge, may also to a certain extent illustrate his different reactions to the changed conditions prevailing during the two periods 1937—39 and 1940—42. As a rule the patient is weighed during the first week of his stay in hospital, and unless there is any special reason to the contrary he is subsequently weighed once a week.

The difference in weight on discharge compared with the weight on admittance to hospital can be seen for the two periods from

Table 7.

The table shows the percentage of unhealed cases within a certain period as revealed by X-ray examination in relation to the total number of unhealed cases in each of the year groups.

Period	4 weeks	5 weeks	6 weeks
1937—1939	82.8	28.1	18.7
1940—1942	85.4	44.7	28.5



Table 8.

Changes in weight on discharge after ulcer cure compared with weight on admittance. GU = gastric ulcers, DU = duodenal ulcers.

Period	No. of cases		Number of cases showing											
			increase of 2—10 kg				no change in weight beyond + 1 to — 1 kg.				decrease of 2—6 kg.			
	GD	DU	GU	%	DU	%	GU	%	DU	%	GU	%	DU	%
1937—39	65	111	41	63	61	55	22	33	44	40	2	3	6	5
1940—42	172	236	98	57	99	42	67	38	128	54	7	4	9	4

Table 8. I have here divided the cases up into 3 groups — one intermediate group covering the cases showing practically no change in weight, and one group on each side of this group showing respectively an increase and a decrease in weight during the ulcer cure.

These figures suggest that, the increase in weight during the later period is smaller than during the earlier period. One factor tending to support this conclusion is that, as pointed out above, the period of treatment is appreciably longer for the later period than for the earlier period. Thus it can be seen that, despite the fact that the ulcer cure is on an average longer for the later period 1940—42, the increase in weight is in this period smaller than for the earlier period 1937—39.

It is interesting, in connection with the patient's weight during the cure itself, to study his weight on admittance to hospital. Obviously, when an attempt is made to determine the value of a course of diet, the patient's condition at the beginning of the cure is of very great importance. The weight on admittance should therefore give some indication as to the patient's general condition upon his entering hospital. By comparing the weight on admittance for the two periods it should be possible to obtain a relatively good idea as to the effect of the war years upon the general condition of ulcer patients.

One old method of determining the patient's normal weight in kilogramme is to take the figure whereby his height exceeds 100 cm, so that if, for example, the patient's height is 160 cm, his normal weight should be 60 kilogramme. It is outside the scope of this

little paper to consider here the correctness of this rule, and in actual fact it does not mean so very much in this present connection. On the basis of this rule I have estimated for both the periods 1937—39 and 1940—42 the average weight upon admission to hospital, and the figures will be found in Table 9. The number of cases in the two periods differs quite considerably here, as data concerning height and weight during the earlier period are often lacking. Comparisons between the two periods can therefore only be made with a certain reservation. It appears from the table that the number of patients with sub-normal weight according to the above-mentioned rule considerably predominates in both the periods. In the 1937—39 period this group forms 76 % of the cases examined, in the 1940—42 period 83 %. There is thus no great difference, contrary to what one might have expected having regard to the general deterioration in diet, which deterioration has been most marked in the case of foodstuffs best suited for bad stomachs.

The changed diet might also have been expected to have an effect on the evacuation of the bowels. I have, however, been unable to find any difference in the tendencies towards obstipation during the two periods.

The situation regarding relapses during the two periods is also, of course, of great interest. Table 10 shows the incidence of relap-

Table 9.

Weight on admission to hospital. Weight calculated in accordance with the rule mentioned in the text.

Year	No. of cases where details of weight and height supplied	Weight below estimated normal weight						Weight above estimated normal weight				
		Num-ber	%	<5 kg	>5 kg	>10 kg	>15 kg	Num-ber	<5 kg	>5 kg	>10 kg	>15 kg
1937	26	22	84	5	7	4	6	4	1	0	1	2
1938	15	12	80	3	3	3	3	3	1	1	0	1
1939	15	9	60	0	4	4	1	5	3	0	2	0
	56	43	76	8	14	11	10	12	5	1	3	3
1940	64	48	75	5	15	14	14	15	8	4	0	3
1941	105	91	87	23	28	12	28	10	5	3	1	0
1942	156	132	85	23	36	29	34	17	11	5	1	0
	325	271	83	51	79	65	76	42	24	12	2	3

ses for each year and the number of relapses suffered by one and the same patient. As before, the periods differ considerably as to the number of cases, but it should nevertheless be possible to draw certain conclusions from this table.

As regards duodenal ulcers, the percentage of relapses is approximately as large for both periods, i.e. circa 50%. The percentage of cases in which one relapse occurred is roughly the same (slightly over 60 %) and the percentage of cases in which two relapses occurred is also much the same (about 24 %) in both periods. As to gastric ulcers, a certain difference between the two periods can be detected. During the years 1937—39 relapses occurred in only about 33 % of the cases, while during the years 1940—42 the percentage was 47. The difference appears to be clear, but a statistical test shows that it is not a statistical certainty. One fact worth observing, however, is that the increased incidence occurs during each of the years between 1940 and 1942. The two periods show much the same result regarding the number of relapses suffered by one and the same individual. The tendency to relapse on the part of the ulcer cases which have been studied has therefore probably not become greater in recent war years.

Table 10.

Ulcer relapses during the periods 1937—39 and 1940—42. GU = gastric ulcers, DU = duodenal ulcers.

Year	No. of cases		No. of relapses		% of relapses		Relapses											
							I		II		III		IV		V		VI	
	GU	DU	GU	DU	GU	DU	GU	DU	GU	DU	GU	DU	GU	DU	GU	DU	GU	DU
1937	33	52	10	22	30	42	6	16	2	5	2	1	0	0	0	0	0	0
1938	24	41	9	19	37	45	4	13	3	4	0	1	0	1	1	0	1	0
1939	21	39	7	26	33	62	6	16	1	6	0	3	0	1	0	0	0	0
	78	132	26	67	33	50	16	45	6	15	2	5	0	2	1	0	1	0
							61%	67%	23%	22%								
1940	44	65	22	28	50	43	15	16	4	8	1	2	1	2	1	0	0	0
1941	59	79	27	36	46	45	15	21	7	10	3	4	1	0	1	1	0	0
1942	78	122	36	63	49	50	19	41	12	15	3	5	1	1	0	1	1	0
	181	266	85	127	47	47	49	78	23	33	7	11	3	3	2	2	1	0
							57%	62%	27%	26%								

Table 11.

Relapses of gastric and duodenal ulcer cases. Interval between relapse and first appearance of illness.

Year.	No. of relapses	Relapse after					
		1 year	2 years	3—5 years	6—10 years	11—20 years	over 20 years
1937	32	18	5	1	4	3	1
1938	28	10	6	6	4	2	0
1939	33	10	9	9	3	2	0
	93	38	20	16	11	7	1
		40%	21%	17%			
1940	50	12	12	11	6	6	3
1941	63	15	10	17	11	8	2
1942	99	39	20	19	12	7	2
	212	66	42	47	29	21	7
		31%	20%	22%			

Another question which it is important to consider is whether relapses have occurred at shorter intervals during recent years and whether it is possible to detect just in these war years an increase in the number of relapses at short intervals in relation to the previous attack of ulcer trouble. For the sake of clarity Table 11 has been inserted. It appears from this table that there is no such difference between the two periods. In 61 % and 51 % of the cases respectively relapses occurred one year after the previous attack, and in 21 % and 20 % respectively two years after the same time.

*The investigation has therefore undoubtedly shown that gastric ulcers and duodenal ulcers treated with the ulcer cure have healed more slowly in recent war years than during the immediately preceding peace years. The treatment of ulcer illnesses has not undergone any change during the period reviewed here, 1937—42, other than that occasioned by the rationing of foodstuffs and especially those items of diet of importance to the ulcer cure. The ulcer cure has therefore, on the whole, been carried out according to the same principles throughout the entire period from 1937 to 1942. Accordingly, if one disregards psychical elements, there are in the main only two factors which could be associated with the deterioration in healing*

and they are in the first place the patient's condition on admittance to hospital i.e. at the beginning of the cure, and in the second place the change in the actual diet.

The patient's condition on admittance to hospital can in this material only be judged by a study of the weight. As I have shown above, it was not possible here to deduce any certain difference between the two periods. There are, however, many factors connected with the general condition which it is impossible to judge by anything as simple as the weight, for example the vitamin and salt balance. It is obvious that an impaired vitamin balance upon admittance to hospital may greatly affect the result of the ulcer cure. Such niceties cannot, however, be studied in this material.

The diet during the cure is the other important factor in connection with this question. During the war years the ulcer diet has undergone certain striking changes. Before the war the diet was based mainly on the two important foods, eggs and cream. The daily included 4—6 eggs and 600—800 gramme of thick cream (22—33 %, often more). The greater part of the calory requirements, probably at least 2000 calories, was covered, then, by eggs and cream. Owing to the necessity for rationing, these daily portions have had to be successively reduced during the war years, so that by 1942 the diet included only 1 — (3) eggs and 50 — (200) gramme of cream with a considerably lower fat content than previously (maximum 15 %). In this reduced diet cream and eggs have played a subordinate part and now supply only about 500 calories. There is thus a great difference between the nutritive value of pre-war diet and the present ulcer diet. In addition, butter has also reduced to about half of the previous portion, and moreover has, as a rule, been mixed with margarine ( $\frac{1}{3}$ — $\frac{1}{4}$ ). Apart from the caloric value of eggs and cream in the ulcer diet, the diet's vitamin and salt content is also, of course, of very great interest. According to an investigation carried out by Dr Axel Blomberg at the Serafimer Hospital, the wartime ulcer diet contains too few of the vitamins  $B_1$ , the P—P fraction of  $B_2$  and C. The diet during the earliest stage of the cure, moreover, contains too few A and D vitamins. It is clear that this vitamin deficiency is to a great extent due simply to the reduction in eggs and cream in the diet. Eggs and cream are rich in A and  $B_1$  vitamins. The P-P fraction on  $B_2$  is found in great abundance in eggs. As regards salts, on the other hand, the ulcer diet seems at present to contain adequate quantities.

The importance of the nature of the diet, and particularly of its vitamin content, in ulcer cases has been stressed by many authors (including Alstedt, Archer and Graham, Christianssen, Hauke, Kohn, O'Mullane). *It seems to me to be clear from my material that, while a deterioration in the healing of the sores can be observed, it can also be seen at the same time that the vitamin balance is tending to be upset to an increasing degree.*

### Conclusion.

The ulcer material at the Serafiner Hospital's Medical Policlinic from the years 1930 to 1942 show no certain increase in incidence for the latter part of the period. On the other hand, the number of cases admitted to and treated at the Hospital has clearly increased during recent years owing to the difficulties of diet at home. The period of treatment has become longer during the war years 1940—42 in comparison with the period 1937—39, and this seems to be due to the fact that healing took place more slowly during the period 1940—42, which in turn is shown to be due to a deterioration in healing as established by X-ray examination. In both periods, however, about 60 % of the cases have healed upon the completion of the ulcer cure. The difference in the treatment of ulcer cases during the two periods 1937—39 and 1940—42 may be attributed solely to the changes in diet which have been rendered necessary by rationing. These changes have consisted chiefly of a deterioration in the calorific value of the diet and of a reduction in its vitamin content.

### Bibliography.

- Alstedt, G.: Studier over mavesårets hyppighet. N. M. T. 15, 168, 1938: 16, 1946, 1938: 1, 157, 1939. — Archer, H. E. and Graham, G.: The subservŷ State in Relation to Gastric and Duodenal Ulcer. The Lancet 230, 364, 1936. — v. Bergmann, G., und Katsch, G.: Magen- und Darmgeschwür. Handbuch der normal. und pathol. Physiologie III 1927. — Busch, F.-A.: Das Ulkusproblem. Münch. Med. Wochenschr. 87, 1354, 1940. — Christianssen, J.: Mavesaar og Folkenæring. N. M. T. 16, 2040, 1938. — Cohnheim, P.: Beitrag zur Diagnostik und Ätiologie der Magen- und Zwölffingerdarmgeschwüre. Arch. Verdgschrkh. 27, 241, 1921. — Hansen, J.: Undersøgelser over frekvensen av ulcus ventriculi s duodeni. Ugeskr. f. Læger 99, 1145, 1937. — Hansen, J., Pedersen, S. and J.: Om

Ændringer i Ulcussygdomen. N. M. T. 12, 2933, 1941. — Hauke, H.: Experimentelle Erzeugung und Pathogenese von C-Vitaminmangelgeschwüren des Magens. Klin. Wochenschr. 16, 1205, 1937. — Holmgren, I.: Serafimerlasarettets ulcusmaterial 1914—1934. Sv. Läkarsällsk. förhandl. 1936. — Kalk, H.: Magen- und Duodenalgeschwür. Neue Deutsche Klinik 6, 1930. — Kohn, B.: Peptic Ulcer a Deficiency Disease? ref. Die Vitamine, 9, 1943. (Brit. med. J. 489, 1943). — Madelung, W.: Häufigkeit und Folgezustände von Magen- und Duodenalgeschwüren. — Malmros, H. and Björhn, R.: Kristidens inverkan på magsårets läkning. Sv. Läkartidn. 40, 1669, 1943. — Mattisson, K.: Das Magengeschwür. Akad. avh. Lund 1931. — Moynihan, B.: Duodenalsåret. Stockholm 1916. — Nicol, B. M.: The geographical distribution of gastric and duodenal ulcers in the British Isles. Brit. Med. J. 2, 780, 1941. — O'Mullane, J. J.: Peptic Ulcer a Deficiency Disease? ref. Die Vitamine, 9, 1943. (Brit. Med. J. 302, 1943). — Weidinger, A.: Geschlechts-, Alters- und Berufsverteilung beim Ulcus ventriculi und duodeni. Münch. med. Wochenschr. 87, 882, 1940. — Wiebel, K. and Kunstreich, W.: Die Alters- und Berufsverteilung der Magen- und Zwölffingerdarmgeschwüre. Münch. med. Wochenschr. 87, 94, 1940.

---

(Communication from Medical Ward B, Centralsygehuset, Slagelse,  
Denmark. Senior Physician: H. Aastrup, M. D.)

## Is there a Primary, Acquired Hemolytic Jaundice?

Communication of a Supposed Case and some Investigations  
into the Erythrocytes.

By

AAGE KIRKEGAARD and GERTRUD KIRKEGAARD..

(Submitted for publication October 27, 1944).

---

One of the most conspicuous features of the first descriptions of the chronic hemolytic jaundice is its marked heredity. Among other things it will appear from the titles of the first descriptions by Wilson (127) «Some Cases Showing *Hereditary*<sup>1</sup> Enlargement of the Spleen», 1890, and Minkowski (90) «Über eine *hereditäre*<sup>1</sup>, unter dem Bilde eines chronischen Ikterus mit Urobilinurie, Splenomegalie und Nierensiderosis verlaufende Affektion», 1900. Each of these authors reports the case of a family with 6 and 8 cases respectively in 3 generations. It may be mentioned as a matter of curiosity that already Vainlair and Masins (117), 1871, and Mur-chinson (93), 1877, reported cases of a disorder that doubtless was hemolytic jaundice and which was also hereditary.

But already before the end of the 19th century and just after the beginning of the 20th communications were published, especially by French authors, of cases in which it has been impossible to trace any heredity [Chauffard (8), Hayem (19), Vidal, Abrami and Brulé (126)], and as Vidal and collaborators moreover succeeded in producing the cardinal symptoms of hemolytic jaundice in experiments — anemia, jaundice, enlargement of the spleen, reti-

---

<sup>1</sup> Italicized by the authors.



culocytosis, and decreased osmotic resistance — by means of injection of hemolysing substances into dogs, it became doubtful whether the heredity of this disorder is obligatory. Two types are simply set up and Chauffard (8) emphasizes the great difference between the very exhausted patients with the acquired form of the disease — *typus Hayem-Widal* — and the almost healthy patients with the hereditary form — *typus Minkowski-Chauffard*.

About 1920, however, the views change once more. After very thorough examinations Gänsslen (70, 71, 72) points out that the disease may occur in a latent form as the so-called hemolytic constitution, which does not give rise to any clinical symptoms and which, therefore, can only be disclosed through examination of the blood. Therefore examination of the blood of the whole family must be insisted on to make it possible with certainty to establish the diagnosis of acquired hemolytic jaundice. Accordingly reports also appear about cases with a completely negative family anamnesis, in which only the examination of the blood of the members of the family disclosed the heredity [Dawson (61, 62), Ewig (68), Paschkis (98, 99)]. Adler (1) moreover points out that many of the cases reported as acquired are symptomatic or secondary cases, the hemolytic anemia being due to some fundamental disorder, e. g. an infection, an intoxication, or a disease of the blood.

Gradually there was thus a tendency completely to deny the existence of the primary, acquired hemolytic jaundice until, 10—15 years ago, English and German authors reported some cases in which the demonstration of heredity failed despite careful examinations of the blood of the family; nor were signs of any other disorder found in these patients [Adler (1), Davidsohn (9, 10), Freund (14), Gripwall (18), Heilmeyer and Albus (20), Meinertz (24), Röpke (34)].

Thus there seems to be a group of the patients with the acquired hemolytic syndrome in whom no etiological element can be demonstrated. In the present publication we have tried to isolate this group as a »primary» form. It is, however, most likely that future investigations will lead to a differentiation of this group as regards the etiology.

In the following 2 cases of hemolytic jaundice will be reported, of which one is presumably hereditary and the other one acquired, and by means of comparison between these 2 cases and parallels

from the literature we shall try to point out the differences between the two forms to see, if a clinical and hematologic distinction is possible.

### *Case Records.*

*Patient No. 1 (hereditary)* was a housewife, aged 45, married to a printer's foreman. The family anamnesis negative, examination of her mother made hemolytic jaundice probable (see below).

Apart from pleuritis while she was a baby and salpingitis at the age of 43, she was previously in good health. Menstruation natural. From her girlhood she has had periods of anemia, fatigue, vertigo, functional dyspnoea, palpitations, and oppression, especially in spring. 4 months before admission she was in bed for 3 weeks with fever and jaundice, since then she has been tired and weak. Never any anomalies of the bones, brittleness of the nails, or burning of the tongue. The functions are normal.

Objective examination: Moderately pale with a slightly icteric tinge of the skin and the sclerae. She is not exhausted; medium state of nutrition. The spleen is palpated just below the curvature in left lateral position, the liver, too. Otherwise no special findings, especially no glandular swelling, no deformities of bones or nails, no atrophy of the papillae of the tongue, nor any hemorrhagic diathesis.

The state of the blood and the composition of the sternal marrow will appear from Tables 1 a and 2. WR. —, urine — alb., pus, and sugar, — urobilin and — bile pigments. Microscopy of urine: Leukocytes ++ → (+), trichomonads + → —, growth of bacteria. Ewald's test meal  $\frac{3}{4}$  hour 19 + ? ml 24/67, well chymified, — mucus, feces: — — — blood; galactose test: excreted 0.69 g in 6 hours.

The patient was feeling well during her stay in hospital, did not want extirpation of the spleen.

*Patient No. 2 (acquired)* was an unmarried female clerk, aged 19. Family anamnesis negative, examination of both parents, 7 brothers and sisters, and 3 nephews and nieces negative (see below).

Besides ordinary diseases of childhood the patient has, at the age of 10, suffered from Calvé-Perthes' disease and, at the age of 14, from tonsillitis. Menstruation regular, never pregnant, never venereal diseases. Unlike the former patient she has never previously suffered from anemia, but during the last 3 months from increasing fatigue, headache, vertigo, tinnitus, a throbbing sensation in her head, dyspnoea on exertion, and paresthesia in both legs, and at the same time she has noticed that her complexion has become yellowish. Never any burning of the tongue, brittleness of the nails, or tendency to hemorrhages. Her functions otherwise natural.

Objective examination: Very pale with a slightly icteric tinge of skin and sclerae. She is rather lean, looking tired and exhausted. The apex of the spleen can just be palpated on inspiration, the liver cannot be felt. Otherwise natural conditions, especially no glandular swelling, oxycephalia, fraying of the nails, or hemorrhagic diathesis.

Table 1 a.  
State of Blood on Admission.

	Pt. No. 1	Pt. No. 2		Pt. No. 1	Pt. No. 2
Hb	74	38	Leukocytes	7780	9080
Erythrocytes	3.30 mill.	1.52 mill.	Neutrophil rod-shaped nucl. %	5.0	6.0
Col. index	1.05	1.17	Neutrophil segmented nucl. %	75.5	49.5
Vol. %	27	15.5	Eosinophil %	2.0	2.75
Index vol.	0.95	1.28	Basophil %	0	0
Osmotic resist.	0.80/0.46	0.56/0.36	Monocytes %	3.0	8.75
Blood Group	0	A	Lymphocytes %	14.5	31.5
Reticulocytes	15.6 %	39 %	Atypical %	0	1.0
Erythroblasts	(+)	+	Sediment. test mm	22	145
Anisocytosis	+	++	Cloudy layer mm	19	140
Poikilocytosis	(+)	+	Thrombocytes	340.000	66.000
Polychromasia	(+)	++	Icteric index	10	13

The hemoglobin percentage (Hb) was determined with a Zeiss hemometer.

The colour index was computed according to the formula:

$$\text{Index} = \frac{\text{Hb}}{\text{Erythrocyt. mill.} \times 21.4} \quad (\text{Bjerring \& Sørensen}) (52).$$

The volume percentage was determined with v. Allen's hematocrit with Warburg & Christensen's (57, 58) fluid.

The volume index was calculated according to the formula:

$$\text{Index} = \frac{\text{Vol \%} \times 0.116}{\text{Erythrocyt. mill.}} \quad [\text{Jørgensen \& Warburg} (79, 80)].$$

The osmotic resistance was determined according to Meulengracht's (26) methodics with macroscopic reading.

The reticulocytes were counted according to the method stated by Kaj Larsen & Skadhauge (86, 87).

The sedimentation test was made a. m. Westergren. As to «cloudy layer» see text.

The thrombocytes were counted according to Oluf Thomsen's method.

The icteric index was determined with Meulengracht's bilirubinometer.

The state of the blood and the composition of the sternal marrow will appear from Tables 1 a and 2. WR. —, Mantoux —, urine: — alb., pus, and sugar — urobilin and bile pigment. Ewald's test meal  $\frac{1}{2}$  hour: 83 + 28 ml 27/58 fairly well chymified (+) mucus.

As she seems to be too ill for splenectomy she is treated with Exhepa fortior without any effect. Then blood transfusion with transitory effect. After treatment with tablettae ferrosi tartratis  $2 \times 3$  the hemoglobin percentage rises to 58 and the number of erythrocytes to well over 2 mill. per  $\text{mm}^3$ , but just as splenectomy is reconsidered the hemoglobin percentage falls to about 20, the number of erythrocytes to below 1 mill., the temperature rises to  $40^\circ$  and the patient dies in a state of extreme anemia.

### Family Examination.

Both patients stated that none of their families had suffered from anemia or jaundice. As there are compensated forms of the disease, as referred to, the families were examined to the possible extent, hemoglobin percentage, number of erythrocytes, osmotic resistance, number of reticulocytes, and in some of the persons also volume percentage and average diameter being determined.

Of the first patient's 2 brothers and 2 brothers' children none had less than 102 per cent. hemoglobin and none below 4.93 mill. erythrocytes per  $\text{mm}^3$ , whilst the highest reticulocyte percentage was 0.8 (one, however, had 1.4) and the lowest osmotic resistance 0.48 and 0.36 per cent. NaCl (beginning and total hemolysis). The patient's mother had 107 per cent. hemoglobin and 4.99 mill. erythrocytes per  $\text{mm}^3$ , but the reticulocyte percentage was 2.1 and the osmotic resistance 0.50/0.30 per cent. NaCl.

In the other patient both parents, 6 out of 7 brothers and sisters, and 3 nieces and nephews were examined. In one of the latter a simple anemia was found with 81 per cent. hemoglobin and 3.84 mill. erythrocytes per  $\text{mm}^3$ , 0.4 per cent. of these being reticulocytes, osmotic resistance 0.48—0.38. In the other cases over 90 per cent. hemoglobin was found and 4.20 mill. erythrocytes per  $\text{mm}^3$ . The osmotic resistance was not below 0.48—0.38.

For comparison it can be mentioned that in normal individuals beginning hemolysis is found at 0.48—0.42 per cent. NaCl [Hamburger<sup>1</sup>, v. Lienbach<sup>1</sup>, Meulengracht (26), Vaquez<sup>1</sup>, Strauss<sup>1</sup>] and total hemolysis at 0.40—0.38 (Strauss<sup>1</sup>), 0.38—0.32 [Meulengracht (26)], 0.36—0.34 (Ribierre<sup>1</sup>). Thus in none of the persons examined there should be decreased osmotic resistance, apart from the mother of the first patient.

The reticulocyte figures were all below the 1.5 per cent. stated by Kaj Larsen and Skadhauge (86, 87) as the upper physiologic limit. In this respect, too, the first patient's mother is an exception, her reticulocyte figure being 2.1 per cent.

The family examinations thus seem to indicate that the first patient's case is a hereditary one, the second patient's an acquired case, which is in good conformity with the whole of the clinical picture, as will appear from the following.

<sup>1</sup> quot. Meulengracht (26).

### Sex, Age, Initial Symptoms.

Both our patients were women, and according to the literature both hereditary and acquired cases are found somewhat more frequently in women. Among 57 acquired cases in the literature we found 21 men and 36 women.

All age classes are fairly equally represented with acquired cases, from 11 years [Freund (14)] till 69 years [Meinertz (24)] and 77 years [Heilmeyer and Albus (20)]. Baty (49) describes a congenital case and Holten (78) among others a patient «who has always suffered from anemia», both of them with negative family anamnesis. As the families, however, have not been examined with a view to hemolytic jaundice it will doubtless be the wisest thing for the present, like Meulengracht (26), to group these and similar cases separately as «isolated cases».

It is a matter of course that the hereditary cases are always congenital and the time when the disease manifests itself rather occasional.

The symptoms making the patient seek medical advice are most frequently jaundice, or the anemia with its fatigue, dyspnoea and palpitations; but not infrequently it will be the symptoms from the enlarged spleen, such as pain in the left side of the epigastrium or the left hypochondrium, or it may be an uncharacteristic dyspepsia [Foulds (12), Rabinowitz (30), Rastetter and Murphy (31) et al.].

As always in hemolytic anemias the central feature of the facies morbi is, however, the increased transformation of blood. All symptoms can also be ascribed to the increased breaking down of erythrocytes as well as to the increased regeneration. In the former group we find 1) acholuric jaundice, 2) enlargement of the spleen, 3) anemia, 4) decreased average diameter, 5) spherocytosis and decreased «rouleaux formation» in the native preparation, and 6) decreased osmotic resistance. To the latter group must be reckoned 7) increase of the red bone marrow, showing highly increased erythropoiesis under the microscope, 8) the occurrence of erythroblasts, anisocytosis, poikilocytosis, Cabot's ring bodies and Jolly's bodies in the peripheral blood, and 9) reticulocytosis.

### 1. *Jaundice.*

Both our patients were slightly, but distinctly, icteric and on examination with Meulengracht's bilirubinometer the icteric index of the first patient was found to be 14, 10, and 11, while in the second patient it was 13, 15, and 18 rising with the onset of the crisis.

In the literature no great difference is stated between the degrees of jaundice in the acquired and the hereditary forms. Almost all authors state the jaundice to be faint, though fluctuating with the hemolytic crises. In an acquired case Reynolds (32), however, finds an icteric index of 100. Sometimes jaundice is not seen in hereditary cases [Dawson (61), in 10 per cent., Debré, Lamy, See and Schrameck (63) about 25 per cent., Gänsslen (70) 40 per cent., Gripwall (18) 6—8 per cent., Meulengracht (26) 33 per cent., Zimmermann (129) 16 per cent.]. On the other hand bilirubinemia seems to be present in 100 per cent. or nearly 100 per cent. of the cases [Gänsslen (70), Gripwall (18), Meulengracht (26), Debré, Lamy, See and Schrameck (63), Sharpe (111)]. All the cases reported as acquired had jaundice.

In neither form does the jaundice give rise to excretion of bile pigments in the urine, and it is not accompanied by itching of the skin and bradycardia either, the biliary acid not being increased. But in both forms there is a great deal of urobilinuria and the feces contain great amounts of urobilinogen and urobilin.

### 2. *Swelling of the Spleen.*

In both our patients the spleen could just be palpated on deep inspiration.

In the literature there seems to be no difference between the swelling of the spleen in the hereditary and the acquired forms. Most authors agree that swelling of the spleen is doubtless present in all cases, but it is not always palpable. Debré, Lamy, See and Schrameck (63) find a demonstrable swelling of the spleen in all their hereditary cases, whilst others have been unable to palpate the spleen in 15—30 per cent. of the cases [Gänsslen (70), Gripwall (18), Meulengracht (26)]. On splenectomy the spleen, however, often proved to be enlarged in these cases.

In patients with acquired hemolytic jaundice there was swelling of the spleen in all the cases in which the symptom is mentioned. In 2 of 3 cases Heilmeyer and Albus (20) find the swelling of the spleen on percussion and only later on palpation, for which reason they believe that the swelling of the spleen developed late in the acquired form. The swelling increases during bad periods, especially during crises [Gripwall (18), Vaughan (120, 121)]. A very interesting case has been reported by Waugh (39) in which the disease developed 4 years after splenectomy owing to thrombopenia. On post mortem examination a small accessory spleen, weighing 5 g, was found.

After splenectomy or post mortem examination the weight of the spleen has been found to be 700—1200 g [Friedmann and Katz (15), Micheli (27), Peck (28), Röpke (34)], in one case 2200 g [Sack (35)], which corresponds to the weight in hereditary cases.

### 3. *Anemia.*

The anemia was of different degree in our patients. The first patient (hereditary) had 74—88 per cent. hemoglobin and 3.3—3.96 mill. erythrocytes per  $\text{mm}^3$ , whilst the other one (acquired) had 38 per cent. hemoglobin and 1.52 mill. erythrocytes per  $\text{mm}^3$ , increasing under iron therapy to 58 per cent. hemoglobin and 2.2 mill. erythrocytes per  $\text{mm}^3$  and then falling rapidly to 15 per cent. hemoglobin and 0.51 mill. erythrocytes at the patient's death. In the first patient the colour index was 1.05 admission and remained about 1, whilst in the second patient it was constantly increased, 19 out of 20 determinations without blood transfusion showing a colour index of  $> 1.20$ , 11 of them over 1.30.

Already in the first communications in the literature the slight anemia of the hereditary cases (apart from the crises) can be traced as a sharp contrast to the severe anemia of the acquired cases. Thus in 1893 Wilson and Stanley (128) find 50—60 per cent. hemoglobin and 3.3—3.8 mill. erythrocytes per  $\text{mm}^3$  in 6 hereditary cases, whilst in 1898 Hayem (19) finds 0.65—2.8 mill. erythrocytes per  $\text{mm}^3$  in 3 acquired cases. Krumbhaar (84) finds an average of 3.3 mill. erythrocytes per  $\text{mm}^3$  in 103 hereditary cases and 2.03 in 55 acquired (most certainly both primary and symptomatic) cases.

More recent communications have confirmed this. Meulen-

gracht (26) only finds 5 out of 24 hereditary cases with less than 60 per cent. hemoglobin and 3.0 mill. erythrocytes per  $\text{mm}^3$  and Zimmermann (129) only 4 out of 36 cases with less than 2.0 mill. erythrocytes per  $\text{mm}^3$ . Others only find anemia in 50—65 per cent. of the cases [Gripwall (18), Gäusslen (70)], and the degree of the anemia is as a rule stated to be 40—70 per cent. hemoglobin and 2 or 3—4 mill. erythrocytes per  $\text{mm}^3$  [Dawson (61), Debré, Lamy, See and Schrameck (63), Gripwall (18), Gäusslen (70), Sharpe (111)].

The anemia of the acquired cases is stated to be much deeper, only in 3 out of 69 cases found in the literature does the hemoglobin percentage exceed 60 per cent. [Friedmann and Katz (15), Meinertz (24), Sack (35)] and in 14 cases 40 per cent. hemoglobin, and in 7 patients only the number of erythrocytes was found to be over 3.0 mill. per  $\text{mm}^3$  [Brewer (7), Foulds (12), Fowler (13), Friedmann and Katz (15), Lewin (22), Pollitzer, Haumeder and Schoblin (29)]. On the other hand figures as low as 6 per cent. hemoglobin and 0.8 mill. erythrocytes per  $\text{mm}^3$  have been found [Davidsohn (9), Freund (14), Hayem (19)].

In the hereditary cases the colour index is as a rule found to be normal, but both increased and decreased values have been seen [Gripwall (18), Menlengracht (26)].

In the 30 acquired cases in which we found the colour index determined it was too low in 4 cases, normal in 13 cases and too high in 13 cases, right up to 2.0 [Fowler (13)].

In our first patient the volume percentage was 27, in the other 15  $\frac{1}{2}$ , fluctuating with the degree of the anemia, the volume index 0.95 and 1.28 respectively. As the latter figure is distinctly increased the examination was repeated and now 1.25 was found.

In hereditary cases Gripwall (18) finds the volume index to be normal, in one case, however, 1.8. Otherwise examinations into volume percentage and volume index are very scanty; as far as the acquired form is concerned only Fowler (13) states that he finds 24 and 30 vol. % and a volume index of 1.0 and 1.16.

Heilmeyer and Albus (20) have computed the average volume of the erythrocytes and found 81—127  $\mu^3$  and Waugh (39) finds 90  $\mu^3$  in acquired cases, which is a little more than the normal 72—87  $\mu^3$  [Haden (74)] and 83—87  $\mu^3$  [Probst (102): own experiments and average figure of 8 authors].



In our first patient (hereditary) an average volume of  $81.5 \mu^3$  was found, and the other patient (acquired)  $102 \mu^3$ .

According to these examinations the erythrocyte volume seems to be increased in the acquired form and normal in the hereditary form.

#### 4. *The Average Diameter of the Erythrocytes.*

To measure the average diameter we used an ordinary blood-film stained according to Giemsa's method and an eyepiece micrometer. Oil immersion was used and the tube was adjusted so as to make one division correspond to  $1.5 \mu$ ; the results were read with the precision of  $\frac{1}{2}$  division. In each individual 500 erythrocytes were measured, erythrocytes of irregular shape and in clumps not being considered. By means of this method an average diameter of  $7.52 \mu$  was found in controls, in the first patient (hereditary)  $6.61 \mu$  and in the second patient (acquired)  $7.28 \mu$  (Fig. 1 and Table 1 b). In No. 2 a considerably greater standard deviation is seen simultaneously, which is illustrated in the Price-Jones curve as a broader »basis». 13 different authors found the average diameter measured in dry preparations with eyepiece micrometer to be  $7.2$ — $8.15 \mu$ , averaging  $7.73 \mu$  [Mogensen (91)].

The curves of both patients are a little asymmetrical, as there is an increase of the large cells. This is doubtless due to the great amount of reticuloocytes, for in a sample taken at random it appeared that of 100 of these cells, which are basophil in the Giemsa-preparation [Gripwall (18)], 11 measured  $7.7 \mu$ , 19  $8.5 \mu$ , 60  $9.2 \mu$ , and 10  $10.0 \mu$ .

All authors have agreed that the average diameter is diminished in patients with hereditary hemolytic jaundice ever since Chauffard (8) demonstrated this symptom [Bayley and Hawksley (50), Debré, Lamy, See and Schrameck (63), Gripwall (18), Haden (74), Meulengraecht (26), Paxton (100), Vaughan (120), Zimmermann (129)]. Measured according to Price-Jones's method the average diameter is found to be  $6.61$ — $5.96 \mu$  [Hawksley (75) 3 cases, Mogensen (91) 2, Paxton (100) 4].

In patients with acquired hemolytic jaundice the average diameter is stated to be rather varying, from  $6.2$ — $6.9$  [Davidsohn (9), Heilmeyer and Albus (20)] to  $8.0$ — $8.5$  [Duthie (11), Grip-

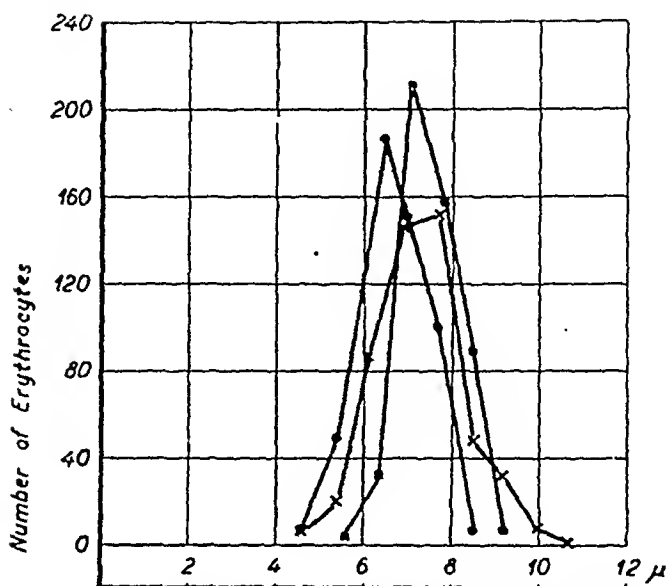


Fig. 1. Measurement of average diameter of 500 Erythrocytes in  
 Pt. Nr 1 —•—•—      Pt. Nr 2 —x—x—      Control —■—■—

wall (18), Meulengracht (26)]. Heilmeyer and Albus (20) found that the average diameter became normal after splenectomy. It is, however, difficult to judge these figures, as it is not always stated which method has been employed, but at any rate it is not a question of a constantly decreased diameter as in the hereditary form.

### 5. Spherocytosis.

Like Gripwall (18) we will define the term spherocytosis as an increase of the thickness of the erythrocytes in proportion to the diameter. It is quite obvious then that the shape approaches that of a sphere. This increase was found in both our patients, which will appear from Table 1 b.

The spherocytosis is one of the most constant symptoms of the hereditary hemolytic jaundice [Gripwall (18), Haden (74), Meulengracht (26), Vaughan (120), Zimmermann (129)] indeed many authors have considered it to be pathognomonic [Gripwall (18), Vaughan (120) et al.]. Both Haden (74) and Vaughan (120) have found the degree of spherocytosis proportional to the decrease of the osmotic resistance, and in a series of fine experiments Haden (74) has shown how in the course of hemolysis the erythrocytes become

Table 1 b.  
Average Size of the Erythrocytes.

	Diameter $\mu$	Volume $\mu^3$	Thickness $\mu$	Thickness: Diameter
Pt. No. 1	$6.61 \pm 0.63^1$	81.5	2.35	0.355
Pt. No. 2	$7.28 \pm 0.95$	102.0	2.47	0.340
Control ....	$7.52 \pm 0.51$	79—88	1.77—1.92	0.236—0.256

The diameter measured in Giemsa-preparation with eyepiece-micrometer.

$$\text{Volume} = \frac{\text{vol. \%}}{100 \times \text{erythroc. per mm}^3} \text{mm}^3 = \frac{\text{vol. \%}}{100 \times \text{erythroc. per mm}^3} \times 10^9 \mu^3$$

The thickness =  $\frac{\text{vol.}}{\pi r^2}$  the erythrocytes being considered a short cylinder the volume of which =  $\pi r^2 \times$  the thickness. ( $r = \frac{1}{2}$  average diameter).

$$^1 \text{The standard deviation} = \sqrt{\frac{\Delta \Sigma^2}{n-1}}$$

gradually more spherical, for which reason he considers the spherical shape a precursory stage of hemolysis. In marked hemolytic jaundice he found the erythrocytes so spherical that their shape was not altered further before the hemolysis. On the basis of these experiments Haden (74) believes the spherocytosis to be the cause of the decreased osmotic resistance, although other elements, too, such as the firmness of the erythrocyte membrane and the structure of the stroma, must play a part.

Measurement of the thickness of the erythrocytes in patients with acquired hemolytic jaundice has previously been made only by Heilmeyer and Albus (20), who find 2.5—3.6, thus a distinct increase. In 2 patients on whom splenectomy had been performed the thickness, however, became normal again, and in one patient on whom splenectomy had been performed Gripwall (18) also found a normal thickness of the erythrocytes. Unfortunately the thickness was not known in this case before splenectomy.

The spherocytosis also manifests itself through alterations in the native preparation, viz. greatly decreased «rouleaux formation» with rough and irregular «rouleaux». This symptom was first demonstrated in 1871 by Vainlair and Masius (117) but has been utterly forgotten since then, until Gripwall (18) found it in all his patients. He considers it of great importance to the diagnosis.

Unfortunately we only became aware of this symptom so late that we had it examined in one patient only, in whom it could be

distinctly demonstrated, but as it is doubtless due exclusively to the spherocytosis there is no reason to believe that it should not be found in both patients.

### 6. *The Osmotic Resistance.*

The osmotic resistance of the erythrocytes was decreased in both our patients, and the decrease varied highly at different times as far as the beginning hemolysis was concerned whilst the total hemolysis was fairly constant. Beginning hemolysis was thus found in pt. No. 1 at 0.56—0.80—0.90 per cent. NaCl and in pt. No. 2 at 0.58—0.58—0.70—0.70 per cent. NaCl, whilst for total hemolysis the values were 0.46—0.46—0.48—0.46 and 0.36—0.34—0.36—0.36 per cent. NaCl.

The resistance was thus lower in the first patient despite her far better condition both clinically and hematologically. In both cases a long series of test tubes were found with quite a faint hemolysis so that the beginning hemolysis showed a comparatively greater decrease than the total, a fact Meulengracht already pointed out.

The decrease of the osmotic resistance, which was first demonstrated by Chauffard (8), is a very constant symptom in the hereditary hemolytic jaundice, is found in 90—100 per cent. of the cases examined [Dawson (61), Debré, Lamy, See and Schrameck (63), Gänsslen (70), Meulengracht (26), Sharpe (111), Zimmermann (129)] and seems to vary somewhat with the patient's condition; the resistance is especially decreased during crises.

Normal resistance is found somewhat more frequently in the acquired form; such cases have been reported by Banti (3, 4), Duthie (11), Fowler (13), Meinertz (24), Rastetter and Murphy (31), Reynolds (32), and Sack (35), but by far most cases behave like the hereditary ones. After splenectomy, on the other hand, we see the interesting fact that whilst in the hereditary form the resistance remains decreased, though it rises a little, it becomes quite normal in the acquired cases [Banti (3), Friedmann and Katz (15), Gripwall (18), Heilmeyer and Albus (20), Lewin (22), Meulengracht (26), Micheli (27)]. This fact might indicate that the spleen plays a more dominant rôle in the pathogenesis of the acquired form than in that of the hereditary form.

### 7. The Bone Marrow.

Both on macroscopic and microscopic examination the bone marrow is marked by the highly increased erythropoiesis. As the macroscopic examination can only be made post mortem we have to refer to the literature as regards this question, but there is hardly any reason to expect any difference between the acquired and the hereditary forms. As can be expected the red marrow is found to be highly augmented [hereditary cases: Meulengracht (26) et al., acquired cases: Davidsohn (9), Duthie (11)], in a few cases the hyperplasia is so marked that lumps of extraosseous marrow, up to the size of a walnut, are found [Dawson (61), Hartfall and Stuart quot. Vaughan (120, 121), Vaughan (120, 121)], most frequently behind the pleura along the lower part of the thoracic column. Rothe Meyer (107), however, succeeded in demonstrating *in vivo* an increase of the diploë by X-raying the skull.

On microscopic examination a highly increased erythropoiesis is seen. On examination of the sternal marrow (Table 2) we found 32.4 per cent. erythroblasts in our first patient and 44.4 per cent. in the second one. For purposes of comparison we state that the normal findings are 6.5—19 per cent. erythroblasts [Arinkin (48): 6.5—19, Gormsen (73): 17.3, Kornerup (83): 15.3, Markoff (89): 13.06, Nordenson (95): 14.4, Plum (101): 14.0, Segerdahl (110): 11.5—12.88], whilst a few authors state higher figures [Klima (82): 26.5, Rohr (104): 31].

If we look at the erythroblasts as compared with «the white system» we find 192 and 318 respectively per 400 «Whites», the normal findings being 50—70 [Videbeck (122)], the erythropoiesis thus being increased by about 3—500 per cent. Similar increases have been found in patients with hereditary hemolytic jaundice by Söeborg Ohlsen and Roelsen (112), de Weerd (41), and Weiner and Kaznelson (124), whilst Töttermann (37), in a presumably acquired case, and Söeborg Ohlsen and Roelsen (112), in an «isolated» case, find an increase of about 2500 per cent. It seems, then, as if there is a more marked erythropoiesis in the acquired form.

Of special interest is the finding of megaloblasts, which was previously considered characteristic of pernicious anemia only. It has been previously observed both in the hereditary form [Dawson

Table 2.  
Sternal Marrow.

	Pt. No. 1	Pt. No. 2		Pt. No. 1	Pt. No. 2
Neutrophil segmented nucleus .....	13.4	11.2	Monocytes .....	0.2	1.7
Neutrophil rod-shaped nucleus .....	11.1	8.5	Lymphocytes .....	6.3	4.6
Neutroph. metamyelocytes ..	9.5	3.8	Plasma cells (lymphocyt.) ..	0.4	0.5
" myelocytes ..	5.4	4.2	Reticulum cells .....	8.2	4.2
" promyelocytes ..	6.4	7.9	Erythroblasts orthochrom. ..	1.3	2.2
Eosinophil mature .....	0.5	1.3	" polychrom. ..	23.4	31.4
" not mature ....	0.9	1.0	" basophil ....	7.7	10.8
Basophil .....	0.0	0.0	" in mitosis ..	0.9	0.8
Hemacytoblasts .....	3.7	4.3	Megaloblasts .....	0.5	0.4
Megakaryocytes .....	0.0	0.2	Atypical .....	0.2	1.0

Pt. No. 1 had 227,200 nucleated cells per mm<sup>3</sup>, Pt. No. 2 172,000 per mm<sup>3</sup>.

Differential count of 1000 cells was made in both patients.

The grouping of the cells was made according to Gormsen's (73) publication.

(61), Söeborg Ohlsen and Roelsen (112), Vaughan (120, 121)] and in the acquired form [Meinertz (24), Töttermann (37)]. It has been supposed possibly to be due to lack of antiperniciosa factor owing to the highly increased erythropoiesis.

### 8. Reticulocytosis.

On admission both our patients had a marked reticulocytosis, the first patient (hereditary) 15.6 per cent. or 0.51 mill. per mm<sup>3</sup>, the other one 39 per cent, or 0.60 mill. per mm<sup>3</sup>. Whilst in the first patient the reticulocyte figure remained rather stationary it rose in the second patient to 60—65 per cent., or 0.8—0.9 mill. per mm<sup>3</sup>, falling towards the exit to about 30 per cent. and 0.2 mill. per mm<sup>3</sup>.

Chauffard and Fiessinger (56), who first demonstrated this symptom, thought it was specific of hemolytic anemias. Later on it proved to be present in any anemia in marked regeneration, though never so intense and lasting as in hemolytic anemias.

In hereditary hemolytic jaundice as a rule 5—15 per cent.

reticulocytes are found and not infrequently 30—40 per cent. [Chauffard (8): 14—18, Debré, Lamy, See and Schrameck (63): 8—20, Gripwall (18): 1.4—35, Meulengracht (26): 1—30, Sharpe (111): 2—34.3, average 10.7, Zimmermann (129): up to 26 per cent.]. As will be seen the reticulocytosis may be absent in a few cases.

In the acquired form still higher figures are most frequently seen, as a rule 20—50 per cent. [Banti (3, 4), Brewer (7), Fowler (13), Gripwall (18), Heilmeyer and Albus (20), Lewin (22), Micheli (27), Rastetter and Murphy (31), Töttermann (37), but they may come fully up to 90—95 per cent. [Baty (49), Davidsohn (9), Meulengracht (26), Reynolds (32)]. Thus there is a considerably greater regeneration in the acquired cases. Still the difference is hardly so great as stated by the percentages, as the absolute figures per mm<sup>3</sup> owing to the low erythrocyte figure in the acquired cases do not show so great a difference.

After splenectomy the reticulocyte figure becomes normal in both forms.

Owing to the great number of reticulocytes the blood of patients with hemolytic jaundice is well suited for examination of these cells. As shown by Gripwall (18), Boström (54), and Valentine (118) the reticulocytes are seen in the native preparation as irregular erythrocytes with concavities and convexities, which constantly change while they are being observed (*hilus forms*). When stained direct under the microscope it can be seen how they are stained into reticulocytes. On reading the sedimentation reaction of blood with many reticulocytes Gripwall (18) moreover noticed a strange, cloudy layer, the height of which was proportional to the number of reticulocytes and which on microscopy proved to contain 80—90 per cent. *hilus forms* besides leukocytes, thrombocytes, and normoblasts. Thus the reticulocytes sank more slowly than the other erythrocytes, which was shown by Gripwall to be due to lacking aggregation.

We have been able to ascertain both *hilus forms* and cloudy layer in both our patients, most marked in the second patient, the cloudy layer being far greater here than in the first patient (Table 1).

Already Chauffard (8) found that the reticulocytes were greater than the other erythrocytes, averaging  $8.18\mu$  in diameter as compared to  $6.3\mu$ . On measuring 100 basophil erythrocytes in Giemsa

-stained preparation we found the average diameter to be 8.97, while in the other erythrocytes it was 7.52.

On differential count of the reticulocytes according to the degree of maturity [Heilmeyer (76, 77), Trachtenberg (116)] the following forms were found in the first patient (hereditary): key form 0.4 per cent., reticular form 17.4 per cent., partly reticular 31.6 per cent., and punctate form 50.6 per cent. The corresponding figures for the second patient were 1, 32, 34, 33 per cent. respectively (500 reticulocytes counted in all). As Kaj Larsen and Skadhauge (86, 87) in normal persons find 0, 0, 15, and 85 per cent. respectively this, too, reflects the extreme regeneration, most marked in the second patient.

### 9. *Other Changes in the Blood.*

The other signs of intense erythropoiesis were also found in both our patients: erythroblastemia, anisocytosis, poikilocytosis, and polychromasia, whilst we were unable to observe Jolly's bodies and Cabot's ring bodies. The alterations were most marked in the second patient (acquired form).

Where these phenomena are referred to in the literature on the acquired cases, they are only lacking in 2 cases, viz. polychromasia in one case [Friedmann and Katz (15)] and poikilocytosis in another [Herapath and Fraser (21)]. The number of erythroblasts per 100 leukocytes is stated to be up to 10 [Chauffard (8), Herapath and Fraser (21), Micheli (27), Töttermann (37)], even right up to 15 [Rastetter and Murphy (31)]. Megaloblasts have sometimes been seen in the blood [Meinertz (24), Töttermann (37), Weber (40)]. As these regeneration phenomena can be found in most severe anemias, though to a less marked degree, they cannot qualitatively distinguish the acquired hemolytic jaundice from the hereditary form, but quantitatively they may give a diagnostic clue.

### 10. *Other Symptoms.*

For the sake of completeness we just want to mention a number of symptoms occasionally described in connection with the hereditary hemolytic jaundice. The most conspicuous symptoms are different anomalies of the bones, especially the »Turmschädel», which Gänsslen (70, 71, 72) considered a feature of the hemo-



lytic constitution but which more recent authors only find as a rather sporadic symptom. In this country Rothe Meyer (107) has described osteoporotic hyperostosis in 3 children with the hereditary form.

Of other symptoms the formation of gall-stones may be mentioned (pigment stones owing to increased formation of bilirubin), which is said to be fairly frequent, ulcer cruris [Vaughan (120)], and corneal anomalies [Debré, Lamy, Sec and Schrameck (63)], which are only rarely seen.

### Clinical Course and Prognosis.

The great difference in the clinical course in our 2 patients is evident. The first patient has been ill since her girlhood with periods of milder anemia, the subjective troubles have been trifling, she has so to speak become accustomed to her disease. On the other hand the second patient has never been ill before and in the course of 3—4 months she develops a severe anemia with corresponding symptoms of insufficiency and dies extremely anemic 6 months after the onset of the disease. Whilst the first patient compensates her great loss of erythrocytes fairly well, the second patient does not succeed in doing so at all.

A perusal of the literature shows a similar difference in the course of the hereditary and the acquired forms, apart from the hemolytic crises. In 1898 Hayem (19) already emphasized the violent character of the acquired form. «C'est une maladie dégloboulisante, et même fortement dégloboulisante» and Chauffard (8) writes about the hereditary form: «The patients are born with the disease, which develops together with them... the organism is accommodated to the constant, mild anemia, they hardly feel ill,» and later on: «The acquired cases are far more serious, the anemia is much deeper, the destruction of the erythrocytes far more massive, often with a striking lack of equilibrium between hemolysis and regeneration.»

More recent authors have, however, set up a more cautious prognosis for the hereditary form owing to deaths reported and the constantly imminent crises [Debré, Lamy, Sec and Schrameck (63), Gänsslen (70), Gripwall (18), Meulengraecht (26)], which seem to be provoked by strenuous labour, infections, psychic traumata

[Gripwall (18), Meulengraecht (26)], and menstruation and pregnancy [Gripwall (18)]. It must, however, be pointed out that in most cases the disease takes a mild course, in many cases it remains latent, cf. Gänsslen's healthy individuals with »hemolytic constitution».

Most frequently the acquired form follows an evenly progressive course, sometimes, however, fluctuating [Rabinowitz (30)], as a rule lasting from some months to a few years. Its grave character will appear distinctly from our case record No. 2 and the enumeration of the symptoms given above. The prognosis without splenectomy is, however, difficult to judge, as nearly all cases reported were operated on and the remaining cases were not after-examined or only defectively so. Out of 12 non-operated cases 8 recovered and 4 died.

### Splenectomy.

Whilst both acquired and hereditary hemolytic jaundice is refractory to any other treatment, the introduction of splenectomy [Banti (3, 4), Eppinger (66, 67)] has greatly changed the prognosis of both forms for the better. According to several great statistics comprising about 830 hereditary cases in all, the primary mortality is only 3—4 per cent. [Gänsslen (70), Cowen, Henschen, Herfarth, Leotta, Patel, Pemberton, Ranzi and Aranzini, all quot. Gripwall (18)] and all of them emphasize the remarkable improvement, as all alterations of the blood revert to standard, except the spherocytosis and the decreased osmotic resistance, which are only slightly improved, simultaneous with complete, clinical recovery. Recidivation is, however, reported in some cases [Citron (5), Oehlecker (96), Roth (106)], in a few cases with exit [Freund (14), Gripwall (18), Kaznelson (81)].

The literature comprises 40 cases of the acquired form recovered after splenectomy, whilst 2 died of recidivation after transient postoperative improvement [Freund (14), Rastetter and Murphy (31)] and 1 patient died 2 days after operation [Davidsohn (9)]. Thus these results do not differ from the experience with the hereditary form. As already mentioned the spherocytosis and the osmotic resistance on the other hand seem to subside in the acquired cases after splenectomy in contradistinction to the hereditary cases.

## Histology of the Spleen,

Previous histologic examinations of the spleen in hemolytic jaundice show, almost in accordance, as their most essential feature a heavy hyperemia of the pulpy tissue [Eppinger (66, 67), Meulengracht (26) et al.], which is identical in acquired and hereditary cases [Thompson (113, 114)]. By means of immediate fixation of pieces of the spleen cut out in the course of operation before removal of the organ Gripwall, however, succeeded in demonstrating an enormous hyperemia of the splenic sinuses, which were highly dilated. From this he concludes that conditions must be such in vivo and considers it as being in favour of the view that the hemolysis in the spleen takes place according to Bergenhem and Fåhræus's endopause theory, rather great amounts of lysolecithin being formed during the stagnation of the blood in the sinus cavities at 38°.

As far as we know similar examinations have unfortunately not been made in patients with acquired hemolytic jaundice.

## Etiology and Pathogenesis.

Since in 1890 Wilson (127) declared that as regards etiology and pathogenesis he was »quite in the dark» 2 main views have been prevailing: One that considers the destructive power of the spleen the most essential and one that considers the erythrocyte anomalies the most important. The first view was endorsed among others by Banti (3, 4), Eppinger (66, 67), Gilbert and Minkowski (90), whilst the second view was advocated by Chauffard (8), Haden (74), Naegeli (94), Vaughan (120, 121), and Widal (125). Gripwall (18) has recently submitted these questions to a thorough examination, for which reason we refer to his publication concerning the hereditary form. After a close examination of the literature and a number of ingenious experiments, to some extent inspired by the »endopause theory» about the destruction of the blood set up by Bergenhem and Fåhræus (51), he arrived at the following conclusions: »1. Die Krankheit hat ihren Grund in einer primären Anomalie der roten Blutkörperchen, die in einer charakteristischen Formveränderung sowie einer herabgesetzten Resistenz nicht bloss gegen hypotone Salzlösungen, sondern auch gegen Lysole-

zithin zum Ausdruck kommt. Diese Eigenart der roten Blutkörperchen ist vererblich. 2. Zu dieser kongenitale Anomalie tritt als ein wesentlicher morbider Faktor eine Steigerung der physiologischen blutzerstörenden Funktion der Milz infolge einer erhöhten Endopausefunktion. Die Milzveränderung, d. h. in erster Linie die Splenomegalie, dürfte sekundär sein, weil das Organ durch die Eigenart der Erythrocyten und ihre dadurch bedingte Minderwertigkeit zu einer Steigerung seiner hämolytischen Funktion gezwungen wird.»

As far as the primarily acquired cases are concerned especially Heilmeyer and Albus (20) have taken an interest in the differences of the pathogenesis from the hereditary cases and, in conformity with Banti (3, 4), Friedmann and Katz (15), Gripwall (18), Lewin (22), Meulengracht (26), and Micheli (27), found that after splenectomy the osmotic resistance became normal. They also found that the spherocytosis disappeared. Heilmeyer and Albus (20) therefore believe that in the acquired cases the spleen is the cause of the spherocytosis and the decreased resistance, possibly through the formation of hemolysins.

On transfusion of normal erythrocytes to our patient with acquired hemolytic jaundice they only «lived» for about  $1/5$ — $1/10$  of their normal lifetime (see the following publication), which also speaks in favour of the dominant importance of the spleen in the pathogenesis.

The recidivations after splenectomy previously referred to seem to indicate that other parts of the reticuloendothelial system may take over the rôle of the spleen as essential pathogenetic element. In cases examined post mortem enlarged liver or accessory spleens have also been found, e. g. in the interesting case reported by Waugh (39) in which the disease developed 4 years after splenectomy.

But which are then the properties of the erythrocytes which the spleen or the reticuloendothelial system should be able to bring out?

### Investigation into the Resistance of the Erythrocytes,

Whilst in the hereditary form of hemolytic jaundice the erythrocytes have been the object of numerous examinations, only quite few investigators have thoroughly dealt with the erythrocytes in the acquired form. In the following we shall account for a series of

Table  
Hemolysis Experiments with

Blood + distilled water	Hemolysis			Average Diameter $\mu$ .			Erythrocyt. Mill.		
	1	2	C	1	2	C	1	2	C
$2\frac{1}{2} + 0$	—	—	—	6.9	7.8	7.6	3.55	1.29	3.92
$2\frac{1}{2} + \frac{1}{2}$	(+)	+	—	7.0	7.8	7.1	2.96	1.01	3.19
$2\frac{1}{2} + 1$	+	+	—	6.75	7.6	7.1	2.59	0.82	2.64
$2\frac{1}{2} + 1\frac{1}{2}$	+	++	+	6.85	7.4	6.8	1.63	0.72	1.94
$2\frac{1}{2} + 2$	++	+++	+++	cannot be read	7.5	6.9	1.11	0.55	1.82
$2\frac{1}{2} + 2\frac{1}{2}$	++	+++	+++	—	7.4	6.6	0.83	0.28	1.33

The average diameter was determined with Bock's halometer.

Erythrocytes, Vol. %, Erythrocytevolume (V) and average thickness (h) as in Tables 1 a) and b).

experiments performed with a view to the recent hemolysis theories by Haden (74) and Bergenhem and Fåhræus (51), as such experiments as far as we know have not been previously performed in acquired cases.

### Resistance on Addition of Distilled Water.

Some years ago Haden (74) showed that if increasing amounts of distilled water are added to normal blood the shape of the erythrocytes will approach the spherical shape increasingly until they burst and hemolysis occurs. From this he concluded that the spherocytosis is a precursory stage of hemolysis. In similar examinations of blood of patients with hemolytic jaundice the erythrocytes that were rather spherical in advance only grew slightly thicker, in severe cases they did not grow thicker at all, and the hemolysis occurred at a weaker dilution.

In order to examine whether our 2 patients showed any difference in this respect we performed similar experiments, but to avoid mechanical lesion we added the water direct to the blood, whilst Haden added it to centrifugalized plasma to which the erythrocytes were added again. Moreover we used citrate-blood Haden (74) heparin-blood. These alterations had no particular effect on the results, as we find much the same values as Haden (74) (Table 3).

## 3.

## Addition of Distilled Water.

Volume %			Average Vol. of Erythroc. $\mu^3$				Average Thickness $\mu$			
1	2	C	1	2	C	Ha	1	2	C	Ha
26	14	35	73	108	88	86	1.95	2.25	2.00	2.00
22.5	15	31	76	135	97	93	1.97	3.10	2.45	2.40
19	11.5	25.5	74	140	99	97	2.04	3.10	2.43	2.40
16	9.5	22.5	98	132	116	101	2.65	3.08	3.18	2.55
12.5	8	18	112	145	100	103	2.96	3.62	2.60	2.80
9	6	15.5	108	(212)	116	116	2.88	(5.0)	3.40	2.90

In this and in the following hemolysis experiments 1 and 2 mean Patient No. 1 and Patient No. 2, and C = Control.

Ha = the values found by Haden (74) for normal erythrocytes.

It will appear from the results given in Table 3 that in both patients and in 1 control the erythrocytes increased in volume and thickness with increasing addition of water.

As could be expected the hemolysis occurred at a weaker dilution in the blood of the patients than in that of the control, most readily in the patient with the acquired form.

In the blood of both patients and in that of the control the hemolysis was preceded by an approximation to the spherical shape.

### Resistance to Heat and Mechanical Influence.

In 1936 Berghem and Fåhræus (51) showed that blood corpuscles in citrate-blood with increased sedimentation rate sink far more slowly when allowed to stand at body temperature; the heat stabilizes the suspension of the blood corpuscles. The cause hereof seemed to be that the erythrocytes became more spherical, aggregation and «rouleaux formation» thus being diminished. Berghem and Fåhræus (51) believed that the approximation to spherical shape was due to an enzymatic process in which a substance, lysolecithin, was separated from the serum and attached to the erythrocytes by which they gradually altered their shape and were hemolysed:

Gripwall (18) has performed corresponding examinations in patients with hereditary hemolytic jaundice and found that the

heat stabilization here is considerably slighter, in severe cases almost discontinued. This corresponds well to Bergenheim and Fåhræus's (51) theory about the occurrence of spherocytosis as a cause of the stabilization, as in the hemolytic jaundice the spherocytes cannot become more spherical than they are and the «rouleaux formation» thus is not much reduced. After splenectomy the heat stabilization was again increased, but in one case of recidivation it again deviated from the standard.

It also falls in herewith that Gripwall (18) found the spherocytes more vulnerable, i.e. more readily hemolysed than normal erythrocytes.

In both patients we have performed a number of experiments, allowing the blood to stand at room-temperature and at 37°, and instead of the stabilization of the blood sedimentation determined by the spherocytosis formation we used the beginning hemolysis as an indicator of the erythrocyte alteration, which seems easier and simpler. In order to judge the share of the erythrocytes and the plasma in the hemolysis we moreover took control blood and after centrifugalization let the erythrocytes change plasmas. As Meulengracht (26) moreover has drawn the attention to the vulnerability of the spherocytes to shaking and as Bergenheim and Fåhræus (18) state that the formation of lysolecithin is said to be very slight or even lacking when the blood is being moved, we combined the experiments with the keeping of blood in movement. For purposes of comparison similar experiments were performed in the first patient. The details of the method were as follows:

After a short stasis ( $< \frac{1}{2}$  min.) 9 parts of venous blood are drawn into a record-syringe containing 1 part of Na-citrate. The citrate-blood is allowed to stand in small test tubes, together with a control sample from a healthy individual, at room temperature, in incubator at 37°, and is kept in movement, a nurse walking about with the sample, which is handed over to the night nurse during the night; thus these samples are never at rest for any long time. At different times it is examined whether there is hemolysis or not. The samples, of course, not to be examined until after centrifugalization. We have tried to judge the degree of hemolysis as trace (+), +, ++, and +++.

The results will appear from Table 4 and distinctly show that the blood of the patients was more readily hemolysed than that of the control, most readily in the patient with the acquired form. Moreover the hemolysis was most marked in the case of

Table 4.

Hemolysis Experiments with the Patients' Blood and Control Blood (C) at Rest and in Movement, at 37° and at Room Temperature (18°).

Hours	Movement			37°			18°		
	1	2	C	1	2	C	1	2	C
6	—	—	—	—	—	—	—	—	—
24	—	+	—	—	—	—	—	—	—
72	+	+	—	+	+	—	trace	+	—
96	++	++	trace	++	+	trace	+	+	—

erythrocytes in movement, less marked at rest and at room temperature.

In the replacement experiments control blood of the same group as the patient's blood was used. After centrifugalization of the samples for 10—15 minutes at a rate of about 2000 revolutions per minute 1 ml of plasma of each kind is run into 6 small test tubes from a pipette and 1 drop of erythrocyte-mush is added, all 4 combinations of erythrocytes and plasma thus occurring 3 times: for keeping in movement, at room temperature, and at 37°.

As will appear from Tables 5 and 6 the erythrocytes seem to be chiefly responsible for the lowered resistance, whilst the importance of the plasma seems to be slight. There was no great difference in the 2 patients. If we consider the way of keeping, the hemolysis is furthered equally at 37° and in movement at room temperature. This seems to be at variance with Fähræus's investigations into normal erythrocytes, and we have been unable to find any explanation hereof.

To obtain a better separation between erythrocytes and plasma we performed the same experiments with «washed» erythrocytes; after running out of the pipette the erythrocytes were suspended in 0.9 per cent. NaCl, centrifugalized once more, erythrocytes and plasma then being mixed as above. In this experiment the plasma seems to have played a somewhat greater part (Table 7), as the patient's erythrocytes in control plasma showed no material difference of resistance from control erythrocytes in the patient's plasma. In this case, too, movement was in all combinations of greater importance to the hemolysis than heating.

In order to examine whether the heat hemolysis and the hemo-



Table 5.

Hemolysis Experiments with Erythrocytes of first Patient and Healthy Individual in Plasma of Patient and Healthy Individual at Rest and in Movement at 37° and 18°.

	Movement				At Rest 37°				at Rest 18°			
	1	1	C	C	1	1	C	C	1	1	C	C
Erythr. ....	1	1	C	C	1	1	C	C	1	1	C	C
Plasma ....	1	C	1	C	1	C	1	C	1	C	1	C
24 hours ..	—	—	—	—	—	—	—	—	—	—	—	—
36 " ..	+	—	—	—	trace	—	—	—	—	—	—	—
48 " ..	+	trace	—	—	+	trace	—	—	—	—	—	—
60 " ..	++	trace	—	—	+	trace	—	—	trace	—	—	—
84 " ..	++	+	trace	—	++	+	—	—	+	trace	—	—
108 " ..	++	+	trace	—	++	+	trace	—	+	trace	—	—
132 " ..	+++	++	+	trace	+++	++	+	trace	++	+	trace	—

Table 6.

Hemolysis Experiments with Erythrocytes of second Patient and Healthy Individual in Plasma of Patient and Healthy Individual at Rest and in Movement, at 37° and 18°.

	Movement				At Rest 37°				At Rest 18			
	2	2	C	C	2	2	C	C	2	2	C	C
Erythr. ....	2	2	C	C	2	2	C	C	2	2	C	C
Plasma ....	2	C	2	C	2	C	2	C	2	C	2	C
24 hours ..	—	—	—	—	—	—	—	—	—	—	—	—
36 " ..	trace	trace	—	—	trace	—	—	—	—	—	—	—
72 " ..	+	+	—	—	+	+	—	—	trace	trace	—	—
96 " ..	+	+	clot	trace	+	+	—	—	trace	trace	—	—
120 " ..	++	+	—	trace	++	++	trace	—	trace	trace	—	—
144 " ..	++	++	—	trace	++	++	trace	—	trace	trace	—	—
9 days ..	++	++	—	+	++	++	trace	trace	trace	trace	—	—

Table 7.

Hemolysis Experiments as in Table 6 with «Washed» Erythrocytes.

	Movement				At Rest 37°				At Rest 18°			
	2	2	C	C	2	2	C	C	2	2	C	C
Erythr. ..	2	2	C	C	2	2	C	C	2	2	C	C
Plasma ....	2	C	2	C	2	C	2	C	2	C	2	C
3 hours ..	—	—	—	—	—	—	—	—	—	—	—	—
24 " ..	+	trace	trace	trace	—	—	—	—	—	—	—	—
48 " ..	++	+	+	+	trace	—	—	—	—	—	—	—
72 " ..	+++	++	++	++	trace	trace	trace	—	—	—	—	—
96 " ..					+	+	trace	—	—	—	—	—
120 " ..					++	+	+	trace	—	—	—	—
144 " ..					++	++	+	+	—	—	—	—
12 days ..									trace	trace	—	—
14 days ..									trace	trace	trace	—

Table 8.

Hemolysis Experiments with Determination of the Average Thickness of the Erythrocytes.

At Rest at 37°.

Hours	Hemolysis		Average Diam. $\mu$		Erythr. mlll.		Vol. %		Erythr. Average vol. $\mu^2$		Average Thickness $\mu$	
	2	C	2	C	2	C	2	C	2	C	2	C
0	—	—	6.94	6.85	1.15	3.82	15	30	130	79	3.45	2.13
12	(+)	—	6.84	6.87	2.29	2.54	38	24.5	165	96	4.45	2.58
36	++	—	6.81	6.76	1.74	2.39	22	19	125	79	3.45	2.06
72	+++	++	6.77		1.55		14		90		2.5	
In Movement.												
0	—	—	6.94	6.85	1.15	3.82	15	30	130	79	3.45	2.13
12	+	—	6.87	6.87	2.52	2.18	29	21	115	96	3.12	2.6
36	++	+	6.77	6.82	2.30	2.42	21	21	91	86	2.54	2.46
72	++++	++		6.77	0.15	1.97	2	20½	133	104		2.90
96	clot	+++		7.07		1.88		20		106		2.71
120	*	+++		7.12		1.93		18		93		2.30

lysis brought about mechanically are preceded by an approximation to the spherical shape, like the hemolysis caused by hypotonic solutions, we tried to determine the average thickness of the erythrocytes at various times during the keeping, just as in addition of distilled water. The experiments were performed with »washed» erythrocytes, 8 drops to 1 ml plasma.

Unfortunately the results seem to be a little unreliable here, especially as regards the enormous thickness found sometimes. As the control blood, however, shows very acceptable values as compared with previous examinations it is still possible that we may arrive at an estimate of the alterations. As will appear from Table 8 first an increase of volume and thickness occurs when the erythrocytes are allowed to stand at 37° and then, when the hemolysis has begun, a decrease. In movement conditions seemed to be very much the same for normal blood, whilst already on the first examination the patient's erythrocytes were rather heavily hemolysed, their thickness then again decreasing. At any rate the experiment does not preclude an increase of thickness before the hemolysis.

Summarizing the results of these hemolysis experiments they show:

1. By hypotonic, thermic, and mechanical influences the erythrocytes of the patients were more readily hemolysed than those of the control blood, most readily in the acquired form.

2. In all cases examined the hemolysis was preceded by an approximation to the spherical shape. (This could not be demonstrated, however, for mechanical influence of the erythrocytes of pt. No. 2 owing to hemolysis having already occurred.)

Whilst the results of hemolysis experiments with distilled water are closely corresponding to Haden's (74) results, there is apparently a striking contrast between our experiments and those of Berghem and Fähræus (51), as at the same temperature we find a considerably greater hemolysis in movement than at rest. We have been unable to find any cause hereof, but our blood samples, which were carried by nurses, may have been at rest for certain periods so that the combined mechanical and lysolecithin effect could be especially powerful. The formation of lysolecithin at room temperature is, however, doubtless so low that the mechanical hemolysis must be supposed to have played the greater part. The temperature in the apron pockets of the nurses may have been slightly over room temperature.

The mechanical hemolysis seems at any rate to be of such a magnitude that it can be supposed to be of importance to the destruction of the erythrocytes in vivo and thus to the pathogenesis of the hemolytic jaundice. The fact that the hemolytic crises seem to be provoked by exertion, fever, pregnancy, and psychic traumata — conditions where the blood must be supposed to circulate more rapidly than normally — also speaks in favour of this view.

### Discussion.

Before proceeding to discuss whether the primary, acquired hemolytic jaundice exists, we shall define this notion as a hemolytic anemia with jaundice, without heredity and without any underlying disorder. Thus all the symptomatic forms are excluded besides the hereditary cases.

The most important objections raised against the maintenance

of the facies morbi are 1) that the disorder is doubtless always symptomatic or 2) still hereditary.

re 1) Hemolytic jaundice has been found in patients with highly different disorders, chiefly infections, intoxications, and diseases of the blood. As instances may be mentioned sepsis [Fredhörj (69), Sacquépée (108)], severe proctitis [Widal, Abrami and Brulé (126)], malaria [Curschmann (60), König (85)], meningitis (Strauss), articular rheumatism [Mosse (92), Naegeli (94)], and chronic infections such as tuberculosis [Landouzy and Gaugerot et al. quot. Brulé (55)], and syphilis [East (64), Edman (65), Oulmont and Boidin (97)]. Moreover in poisoning with lead [Davidsohn (9, 10)], naphthol, and arsenuretted hydrogen [Meyer, Panfick quot. Brulé (55)]. Among diseases of the blood we may mention myeloid and lymphatic leukosis [Paschkis (98, 99), Tixier and Troisier (115), Watson (123)], profuse hemorrhages [Paschkis (98, 99), Watson (123), Widal Abrami and Brulé (126)], and lymphogranulomatosis [Paschkis (98, 99), Watson (123), Widal, Abrami & Brulé (126)], and hepatic disorders [Watson (123)].

As these disorders are so highly different it has been believed that the acquired hemolytic jaundice was only found as a symptom in these and other disorders, and not primarily as an independent disease. The great variety of the diseases may, on the other hand, just be indicative of a simple coincidence between these diseases and a primary acquired hemolytic jaundice.

We succeeded in collecting 69 cases of acquired hemolytic jaundice from the literature in which no other disorder was found in the patients, which was also the case with our patient. Of course it can be objected, as previously done by Adler (1), that there may be an underlying disorder even if it cannot be demonstrated. Unfortunately this view cannot be refuted; it may possibly have been so in some of the 69 cases but hardly in all of them. At any rate it appears to us to be a little far-fetched to deny the existence of the disease on this basis.

re 2) It is difficult to disprove that the cases reported as acquired should still be hereditary. The greatest difficulty is that even if there are no diseased members of the family they may prove to be of a «hemolytic constitution» on closer examination of the blood (cf. Gänsslen (70, 71, 72). Paschkis (98, 99) thus reported 2 cases with a negative family anamnesis in which examinations of the blood dis-

closed the heredity. For the same reason the occurrence of the disease at an advanced age cannot prove anything; for it may be a latent hereditary case that becomes manifest for some reason or other.

During recent years these objections, which have been raised especially by Adler (1), Dawson (61, 62), Gänsslen (70, 71, 72), Vaughan (120, 121) and Zimmermann (129), have been strongly challenged by communications about 11 cases in all, in which heredity could not be demonstrated despite extensive family examinations [Freund (14), Heilmeyer and Albus (20), Meinertz (24, 25), Meulengracht (26), Röpke (34)]. Despite examination of both parents, 6 brothers and sisters out of 7, and 3 nephews and nieces we have not been able to find any heredity either. These cases speak the more in favour of an acquired form, as it is generally agreed that the hereditary form is inherited dominantly.

But even the demonstration of such isolated cases is no absolute proof, as it may be a question of mutation, the heredity only being disclosed in the offspring. It may also be imagined that the family is so small that the heredity fails to manifest itself. Practically there is moreover the difficulty that generally all members of a family cannot be examined owing to absence on a journey, death, or the like.

As it is, therefore, hardly possible at present to give a perfectly valid proof of the existence of the primary, acquired hemolytic jaundice we must be content to examine if the divergences stated above between the cases reported as acquired and those reported as hereditary ones are such as justify the maintenance of the acquired form as an independent disorder.

These differences may be summarized as follows:

- 1) In the acquired form there are no similar cases in the family. At least 69 cases with a negative family anamnesis have been reported previously, 11 of them moreover with a negative result of family blood examination.

- 2) In the acquired form the anemia and the regeneration phenomena are more violent than in the hereditary form.

- 3) Spherocytosis is found in both forms. But whilst most frequently the acquired cases have a normal or increased average diameter and increased cell volume, the hereditary cases have a decreased average diameter and normal cell volume. It is possibly

a consequence hereof that normal osmotic resistance is more frequently seen in the acquired cases. The colour index is most frequently increased in the acquired, normal in the hereditary cases.

4) The course seems to be far more serious in the acquired than in the hereditary cases without treatment.

5) In both forms there is complete clinical recovery after splenectomy, with a few exceptions. But whilst the shape of the erythrocytes, the average diameter, and the osmotic resistance become quite normal in acquired cases, they are only altered somewhat in the hereditary cases.

6) Possibly there is less resistance to mechanical and thermic influences in the erythrocytes of the acquired cases.

Of these differences 2), 4), and 6) might strictly speaking be explained as being especially severe hereditary cases; but it appears to us to be rather improbable that just all the severest cases should have been reported as acquired, especially if they were not so. It has also been believed that they were hereditary latent cases manifesting themselves by coming into crisis. The hemolytic crises, however, generally develop in the course of days, possibly weeks, whilst those reported as acquired cases have generally developed in the course of months or years.

On the other hand the other divergences mentioned seem to point at a profound difference between the two forms, a difference in the structure of the erythrocytes and in the rôle played by the spleen in the pathogenesis of the disorders. It would be desirable to get a further confirmation of the observations made, before the final judgment is given.

Considering this it appears to us that for the time being we must reckon with a primary, acquired hemolytic jaundice. Whether we call it so or, like Paschikis, call it pseudohemolytic anemia is only a dispute of words. The latter term, however, seems to us to be misleading, as both the hemolysis and the anemia are real, indeed very marked, too.

### Summary.

From the end of the 19th and the beginning of the 20th centuries till now at least 69 cases of primary, acquired hemolytic jaundice with negative family anamnesis have been reported; examination of the blood of the families in 11 cases gave negative results.

In the course of time it has been discussed whether these cases were symptomatic or still hereditary.

On analysis of symptoms and course in 2 cases of our own — one hereditary and one acquired case — and cases of both forms found in the literature the following symptoms are found on comparison to be characteristic of the acquired form:

1. No heredity, nor on examination of the blood of the family.
2. Severer anemia and more intense erythrocyte regeneration.
3. Normal or increased diameter of the erythrocytes, the volume and colour index of which are most frequently increased, whilst the hereditary form has a decreased average diameter and normal volume and normal colour index.

4. After splenectomy these alterations subside, as do the decrease of the osmotic resistance and the spherocytosis, completely in the acquired form and only partially in the hereditary form. Thus the rôle of the spleen seems to be greatest in the acquired form.

5. In hemolysis brought about by hypotonic, mechanical, and thermic influences no difference of principle is found in the mode of hemolysis, but in our patient with the acquired form the hemolysis occurred more readily and was more marked than in our patient with the hereditary form.

In the experiments the mechanical hemolysis proved to be of such a magnitude that its importance to the pathogenesis must be considered. Moreover it has become probable that all 3 forms of hemolysis are preceded by an approximation to spherical shape.

Secondary or symptomatic, acquired hemolytic jaundice is reported in a great variety of disorders. In our case and in 69 cases reported it has not been possible to demonstrate any underlying disorder.

The authors then arrive at the result that for the time being we must reckon with a primary acquired form of hemolytic jaundice, even if a proof of it in the strictest sense of the word cannot be given.

### References.

A. Communications about Cases of primary, acquired hemolytic Jaundice. (*Italics: The family examined. If more than one Case is reported the number is stated in parenthesis.*)

1. Adler, A.: Münch. med. Wschr. *I*, 454, 1929. — 2. Adler, A & Bressel, M. (3): Deutsch. Arch. klin. Med. 155, 326, 1927. — 3. Banti, G. (3): Se-

maine med. 32, 265, 1912. — 4. Banti, G.: *ibid.* 33, 313, 1913. — 5. Barton, W. M.: *Am. J. med. Sc.* 140, 239, 1910. — 6. Barjou: *Lyon med.* 122, 1029, 1914. — 7. Brewer, G. E.: *Medical Record*: 90, 1, 1916, II. — 8. Chauffard, M. A.: *Semaine med.* 28, 49, 1908. — 9. Davidsohn, L. S. P. (3): *Quart. Journ.* 543, 1932, I. — 10. Davidsohn, L. S. P.: 0 new cases. *Lancet* 919, 1932, II. — 11. Duthie, E. S.: *Lancet* 1167, 1937, I. — 12. Foulds, E. J.: *Brit. med. J.* 267, 1924, II. — 13. Fowler, W. M.: (6) *Ann. int. Med.* 14, 1838, 1941. — 14. Freund, M.: *Amer. J. Childr.* 43, 645, 1932. — 15. Friedmann, G. A. & Katz, E.: *J. Am. med. Ass.* 67, 1295, 1916. — 16. le Gendre, P.: *Bull. et Mém. de la soc. med. des hôp. de Paris* 37, 112, 1909. — 17. de Gennes, L., Salles, P. & Willot: *ibid.* 53, 394, 1937. — 18. Gripwall, E.: *Zur Klinik und Pathologie des hereditären hämolytischen Ikterus*. Thesis, Uppsala 1938. — 19. Hayem, G. (4): *Presse med.* 121, 1898. — 20. Heilmeyer, L. & Albus, L. (3): *Deutseh. Arch. klin. Med.* 178, 89, 1935/36. — 21. Herapath, C. E. K. & Fraser, A. D.: *Lancet* 435, 1925, II. — 22. Lewin, C. (2): *Deutsch. med. Wschr.* 46, 228, 1920. — 23. Lichtenstein, A. & Terwen, A. J. L.: *Deutseh. Arch. klin. Med.* 149, 102, 1925. — 24. Meinertz, J. (3): *Med. Klin.* 29, 73, 1933, I. — 25. Meinertz, J. (0 new): *ibid.* 29, 539, 1933, I. — 26. Meulengracht, E. (2): *Über den chronischen, hereditären, hämolytischen Ikterus*. Thesis, Copenhagen, 1918. — 27. Micheli, F.: *Wien klin. Wschr.* 1269, 1911. — 28. Peck, Ch. H. (2): *J. Am. Med. Ass.* 67, 788, 1916. — 29. Pollitzer, H., Haumeder, H. & Schoblin, St. (10) *Wien Arch. inn. Med.* 2, 375, 1921. — 30. Rabinowitz, J.: *Inaug. Diss. Königsberg* 1919. — 31. Rastetter, J. W. & Murphy, F. D. (2): *Am. J. digest. des. and nutrit.* 4, 805, 1938. — 32. Reynolds, G. P.: *Am. J. Med. Sc.* 179, 549, 1930. — 33. Renaud, P. A. M.: *Times a. Long Island med. J. cit. folia hämat.* 59, 205. — 34. Röpke, W.: *Zentralbl. f. chir.* 63, 973, 1936, I. — 35. Saek, W.: *Med. Klin.* 27, 1641, 1931. — 36. Stejsal, Ritter von (2): *Wien. klin. Wschr.* 19, 661, 1909. — 37. Töttermann, G.: *Acta med. scand.* 90, 27, 1936. — 38. Warfield, L.: *Wiseonsin med. J. cit. folia hämat.* 48, 137, 1932. — 39. Waugh, Theo R.: *Folia hämat.* 48, 248, 1932. — 40. Weber, F. P.: *Am. J. med. Sc.* 167, 220, 1924. — 41. Weerdt, W. de: *Le sang* 12, 738, 1938. Moreover the Following Cases Reported in Periodicals not at our Disposal: 42. Antonelli, G.: *Polielinico sez. prat.* 46, 1100, 1939. — 43. Black, D. R.: *J. Kansas med. Soc.* 31, 94, 1914. — 44. Bruné, G.: *Clin. med. ital.* 60, 416, 1929. — 45. Lynch, J. H.: *Nebraska med. J.* 17, 71, 1932. — 46. Oettinger, W.: *Bull. et Mém. soc. med. de hôp. de Paris* 26, 391, 1908. — 47. Smith, C. T.: *U. S. Vet. Bur. med. Bull.* 4, 948, 1928.

#### B. Other References.

48. Arinkin, M. J.: *Folia hämat.* 38, 233, 1929. — 49. Baty, J. M.: *Am. J. Med. Sc.* 179, 546, 1930. — 50. Bayley, U. & Hawksley, J. C.: *Lancet* 1329, 1934, II. — 51. Bergenhem, B & Fähræus, R.: *Acta path. & microbiol. seand. Suppl.* 26, 211, 1936. — 52. Bierring, E. & Sørensen, G.: *Ugeskr. f. Læger* 98, 822, 1936. — 53. Bock, H.: *Klin. Wschr.* 12, 1141, 1933, I. — 54. Bostrom, L.: *Nord. med. Tidsskrift* 15, 590, 1938. — 55. Brulé, M. in



- Sergent, E., Ribadcau, D. L. & Babonncix, L.: *Traité de pathologie médie.* XII Foie et pancréas. — 56. Chauffard, M. A. & Ficssinger, N.: *C. r. soc. biol.* 63, 672, 1907, II. — 57. Christensen, J. & Warburg, E.: *Hospitalstidende* 71, 1207, 1928. — 58. Christensen, J. & Warburg, E.: *Acta med. scand.* 70, 286, 1929. — 59. Citron, J.: *Deutsch. med. Wschr.* 79, 1922, I. — 60. Curshmann, H.: *Münch. med. Wschr.* 1390, 1930, II. — 61. Dawson of Penn: *Brit. med. Journ.* 921, 1931, I. — 62. Dawson of Penn: *Brit. med. Journ.* 963, 1931, I. — 63. Debré, R., Lamy, M., See, G. & Schrameck, St.: *Ann. méd.* 40, 251, 1936. — 64. East, C. F. T.: *Proc. roy. soc. med.* 17, part 1—2, clin. sect. 14, 1924. — 65. Edman, V.: *Hygiea (Stockholm)* 80, 433, 1918. — 66. Eppinger, H.: *Berlin, klin. Wschr.* 1509, 1913, II. — 67. Eppinger, H.: *Berlin, klin. Wschr.* 1572, 1913, II. — 68. Ewig, W.: *Deutsch. med. Wschr.* 53, 58, 1927. — 69. Fredbärj, T.: *Acta pædiatrica* 10, 158, 1930/31. — 70. Gänsslen, M.: *Deutsch. Arch. klin. Med.* 140, 210, 1922. — 71. Gänsslen, M.: *Klin. Wschr.* 929, 1927, I. — 72. Gänsslen, M.: *Neue deutsche Klinik* 4, *Ergänzungs.* 607, 1936. — 73. Gormsen, H.: *Knoglemarvsundersogelser*, Thesis, Copenhagen, 1942. — 74. Haden, R. L., «A Symposium on the blood» The University of Wisconsin Press pp. 83—103, 1939. — 75. Hawksley, J. C.: *J. Path. & Bact.* 43, 565, 1936. — 76. Heilmeyer, L.: *Med. Klin.* 35, 201, 1939. — 77. Heilmeyer, L.: *Deutsche Arch. klin. Med.* 171, 123, 1931. — 78. Holten, C.: *Ugeskr. f. Læger* 98, 415, 1936. — 79. Jørgensen, S. & Warburg, E.: *Hospitalstidende* 69, 865, 1926. — 80. Jørgensen, S. & Warburg, E.: *Acta med. scand.* 66, 109, 1927. — 81. Kaznelson, P.: *Wien. Arch. inn. Med.* 7, 87, 1924. — 82. Klima, R.: *Spez. Path. u. Therap. inn. Krankh.* 12, *Ergänzb.* 19, 1937. — 83. Kornerrup, V.: *Nord. Med.* 9, 415, 1941. — 84. Krumbhaar, E. B.: *Am. J. med. Sc.* 150, 227, 1915. — 85. König, L.: *Klin. Wschr.* 1584, 1924, II. — 86. Larsen, Kaj & Skadhauge, K.: *Folia hæmat.* 65, 339, 1941. — 87. Larsen, Kaj & Skadhauge, K.: *Ugeskr. f. Læger* 103, 771, 1941. — 88. Lyngar, E.: *Nord. Med.* 14, 1246, 1942. — 89. Markoff, N.: *Deutsch. Arch. klin. Med.* 180, 530, 1937. — 90. Minkowski, O.: *Verh. d. Kongr. inn. Med. Wiesbaden* 1900 pag. 316. — 91. Mogensen, E.: *Studies on the size of the red blood cells*. Thesis, Copenhagen 1938. — 92. Mosse, M.: *Berlin, klin. Wschr.* 50, 684, 1913, I. — 93. Murchinson, C.: *Diseases of the liver* 426, 1877. — 94. Naegeli, O.: *Verh. d. Kongr. inn. Med.* 520, 1928. — 95. Nordenson, N. G.: *Nord. Med.* 6, 834, 1940. — 96. Oehlecker: *Zentralblatt f. chir.* 47, 594, 1920. — 97. Oulmont & Boidin: *Presse med.* 20, 525, 1912. — 98. Paschkis, K.: *Z. klin. Med.* 105, 301, 1927. — 99. Paschkis, K.: *Wien. klin. Wschr.* 43, 166, 1930, I. — 100. Paxton, W. T. W.: *Arch. Dis. Childr.* 10, 421, 1935. — 101. Plum, P.: *Clin. & exper. invest. in Agranulocytosis*. Thesis, Copenhagen & London 1937. — 102. Probst, E.: *Deutsch. Arch. klin. Med.* 180, 539, 1937. — 103. Rohr, K.: *Neue deutsche Klinik* 14, 498, 1937. — 104. Rohr, K.: *Das menschliche Knochenmark*, Leipzig 1940. — 105. Rosenthal, T.: *Deutsche med. Wschr.* 46, 574, 1920. — 106. Roth, O.: *Folia hæmat.* 35, 1, 1927/28. — 107. Roth Meyer, A.: *Ugeskr. f. Læger* 105, 896, 1943. — 108. Sacquépée, E.: *Bull. et mém. de soc. med. Paris* 31, 361, 1908. — 109. Sandström, O.: *Hygiea (Stockholm)* 88, cit. Fredbärj. —

110. Segerdahl, E.: *Acta med. scand. Suppl. 64*, 1935. — 111. Sharpe, J. C.: *Ann. int. med.* 14, 953, 1940. — 112. Søeborg Ohlsen, A. & Roelsen, E.: *Ugeskr. f. Læger* 105, 1125, 1943. — 113. Thompson, W. P.: *John Hopk. Hosp. Bull.* 51, 365, 1932. — 114. Thompson, W. P.: *J. Am. med. Ass.* 107, 1776, 1936. — 115. Tixier & Troisier: *Gaz. de Hop.* (cit. Meulengracht) Febr. 1912. — 116. Trachtenberg, F.: *Folia hæmat.* 46, 1, 1912. — 117. Vainlair, C. F. V. & Masius, J. B. N. V.: *Extr. d. Bull. d. l'Acad. Roy. de med. de Belge cit. Zentr. bl. f. d. med. Wissenschaft* 9, 826, 1871. — 118. Valentine, F. C. O.: *J. path. & bact.* 31, 473, 1928. — 119. Vaquez, A. & Giroux: *C. r. soc. méd. hôp. de Paris* 8/11 1907 cit. *Semaine méd.* 27, 551, 1907. — 120. Vaughan, J. M.: *The Anæmias*, Oxford med. publ. 229, 1932. — 121. Vaughan, J. M.: *J. path. & bact.* 45, 561, 1937. — 122. Videbæk, Aa.: *Folia hæmat.* 65, 203, 1941. — 123. Watson, J.: *Ann. int. med.* 12, 1782, 1938/39. — 124. Weiner, W. & Kaznelson, P.: *Folia hæmat.* 32, 233, 1926. — 125. Widal, F.: *Semaine méd.* 27, 586, 1907. — 126. Widal, F., Abrami, P. & Brulé, M.: *C. r. soc. biol.* 72, 694, 1912. — 127. Wilson, C.: *Clin. soc. transact.* 23, 162, 1890. — 128. Wilson, C. & Stanley, D.: *Clin. soc. transact.* 26, 163, 1893. — 129. Zimmermann, O.: *Wien. klin. Wschr.* 958, 1932.
-

the years 1937—1942. *It comprises only cases in which the diagnosis ulcer has been confirmed by X-ray examination.* In consideration of the statistical side of the work, I have not included patients domiciled outside Stockholm proper. *My material is therefore exclusively that of a large city.*

So far as the male patients is concerned, the difficulties of determining the exact occupations have generally been surmountable. In the case of the female clients, on the other hand, it has not been possible to fix their occupations in more than  $\frac{1}{3}$ rd of the cases. In spite of this defect in the material, I have tried to deal with the female cases having specified occupations in the same way as with the male cases, by placing them in occupational groups.

I shall begin with the male material, since from an occupational point of view it's construction is better, and my treatment of it will therefore be more extensive.

#### *I. Occupational conditions of the male patients.*

The male material comprises 751 patients suffering from gastric ulcer and duodenal ulcer. Their occupations have been recorded, and then tabulated (tables I and II) on the lines of the tabulation of the Statistical Year-Book. The occupations have thus been classified in groups and these groups have been formed into larger units. In certain cases the occupations were not sufficiently specific to be placed in any particular groups, but were of such a nature that they could be included in the larger units.

The tables have been so arranged that the first column indicates the number of workers within the different groups (acc. to the Swedish Statistical Year Book for 1930). The next column contains the number of patients who have visited the Serafimer Hospital's medical polyclinic during 1937—42, and the third column shows the number of ulcer cases. The three following columns give comparative figures, the first indicating the total number of patients at the clinic in relation to the number of workers, the second the number of ulcer cases in relation to the number of workers, and the third the relation between the number of ulcer cases and the total number of cases treated at the clinic.

What first attracts our attention is the relation between the number of visitors to the clinic and the number of workers. It will be seen that the figures vary between 1.56 and 15.9 %. Three of the

to light and heat, and chills, have also attracted some interest in the ulcus genesis (Cf. Cohnheim, v. Bergmann, Einhorn, Ellinger, Heissen, Gebhardt-Richter, Moynihan).

It has also been believed that these exogenous factors could be traced by studying the occupational conditions of the patient, on the assumption that the latter's occupation might in some way cause predisposition to ulcus, partly on account of the nature of the work itself, and partly owing to irregular and unsuitable meals and ways of living necessitated by the patient's work. Hitherto, research along these lines has not produced any positive information on this question. There are moreover only a few books which deal with the problem at any length; in most cases the occupational conditions are dealt with cursorily. Statistics on any large scale are rare. Neither Adler, Wiebel nor Kunstreich found in their investigations any occupations which were conducive to ulcus; all occupations were represented in equal numbers. Mattisson gives remarkably high frequency figures for persons engaged in domestic work. Ahlstedt finds a high frequency of ulcus amongst physicians, leading men in trade and communications, and office personnel in higher positions. He finds it more seldom amongst labourers and artisans; still less frequently amongst retailers, hotel and restaurant staffs, and very rarely indeed amongst persons in the free professions, lower-grade office workers, and amongst the rural population. Both Ahlstedt and Weidinger consider that ulcus occurs less frequently in such occupations as allow of the individual's leading a regular life, and in which the work is not unduly hurried -- in other words, amongst people with whom physical labour predominates over mental strain. The hygienic conditions at the place of work are also regarded as being of importance (Reichert).

A study of the literature on this subject shows, therefore, the significance of occupational conditions has not been satisfactorily investigated. Yet it is easily conceivable that such external conditions may play a part in the development of ulcus. It is mainly men and women in their best years of from 20 to 50 who are prone to ulcer. It seems to me, therefore, that it might be of interest to investigate these conditions more closely.

It is, however, not so easy to obtain suitable material for an investigation of this problem. The material which I present here derives from the medical policlinic of the Serafimer Hospital during



Table 1.

Occupational conditions of 751 male ulcer patients domiciled in Stockholm and treated at the Serafimer Hospital during 1937—1942:

	No. of Workers in Stockholm acc. to the Swedish Statistical Year Book for 1930 (a)	Total No. of Patients at the med. polielinie during 1937—42 (b)	No. of Ulcer cases during 1937—42 (c)	b in % of a	c in % of a	c in % of b
Group I Agriculture + subsidiary occupations .....	2124	339	13	15.96	$0.61 \pm 0.17$	$3.8 \pm 1.04$
Group II Industry and handierfts ....	81416	6950	409	8.45	$0.50 \pm 0.008$	$5.9 \pm 0.28$
Group III Trade and Communications ....	59289	4027	194	6.79	$0.32 \pm 0.022$	$4.8 \pm 0.34$
Office workers in groups I and III	19078	821	54	4.09	0.26	6.5
Group IV Public services and the free professions .....	19954	491	74	2.46	$0.37 \pm 0.042$	$15.1 \pm 2.6$
Group V Domestic work ..	647	54	5	8.33	0.77	9.2
Group VI Ex-workers and others .....	7792	122	2	1.56	0.02	1.6
Total	191300	12804	751		$0.39 \pm 0.015$	

values are around 7—8 %, one is very high, two are low. The fact that we find low figures in groups IV and VI is understandable, since these groups comprise individuals in administrative posts and the free professions: rentiers, property owners, academicians and persons in receipt of pensions, none of whom would be expected to visit a public polielinie to any great extent. The only point worthy of remark here, then, is that patients belonging to group I

— agriculture and subsidiary occupations — visit the clinic in very much larger numbers than those of other groups. This group, however, is a fairly small one.

In the last column, in which the relation between ulcus cases and visitors to the polielinie has been calculated, we find in groups I—III a ratio of about 4—6 %. In the group »administrative services and the free professions», on the other hand, we find the high figure of 15 %; in group V the comparatively high figure of 9.2 %, whereas group VI gives a very low figure. What, then, does this signify in relation to the column we have just studied? For group IV, the figure there was low, but here, this figure is the highest. Consequently, of the visitors to the polielinie in this group, a proportionally very large number were ulcus cases. The actual position is probably this, that patients belonging to group IV do not as a rule visit the polielinies, but when they do, they have probably been sent to the polielinie by their private physician for special and X-ray examinations. In view of the small numbers contained in groups V and VI, we may disregard them. Nor can we expect to find any large numbers of ulcus cases in group VI, since this group comprises almost exclusively people who are well on in years.

The question then arises — is there no real explanation behind the high frequency found in group IV? To be able to answer this we have to study the last column but one in the table, where the relation between ulcus and workers is given. Except in groups V and VI, the frequency figures here vary between 0.32—0.61 %, i.e. within very narrow limits. Group IV gives us the very low figure of 0.37 %. This would not seem to indicate that there is anything special about it as regards frequency, but it is a very difficult group to judge for the very reason that its members visit the polielinie in such small numbers.

In order to try to make the position still more clear, I have set up table No. 2. In this table each group is divided into smaller, more closely specified units. Only in two sub-divisions of group IV do the figures for the frequency of patients, approach the average, namely, in the sub-divisions religion and literature, art, etc. The first of these shows low relative figures everywhere (the group contains only one case of ulcus). The second, on the other hand, shows that no less than 17.3 % of the visitors suffered from ulcus, and the total frequency for ulcus is  $0.99 \pm 0.15$ , which is excep-

Table 2.

Occupations	No. of workers in Stockholm acc. to Stat. Year Book. (a)	No. of patients at the med. policlinic during 1937—42 (b)	No. of ulcers cases during 1937—42 (c)	b in % of a	c in % of a	c in % of b
Group I .....	2124	339	13	15.96	0.61	3.8
Agriculture + subsidiary occupations .....	1416	331	10		0.71	3.0
Fishing + shooting ....	6	6	3			
Group II — Industry ..	81416	6950	409	8.54	0.50	5.9
ore-mining, machine, metal .....	22814	1372	79	6.01	0.34	6.0
quarrying, stone .....	1121	135	6	12.04	0.53	4.4
timber .....	2982	7	1	0.24	0.03	—
paper, printing .....	6924	335	29	4.84	0.42	8.6
(especially typographers)	5131	266	24	5.18	0.41	9.0
food, beverages, tobacco	6317	258	18	4.08	0.28	6.9
textile, clothing .....	3424	225	10	6.57	0.29	4.4
rubber .....	3926	218	20	5.55	0.51	9.1
chemical, technical ....	1517	24	2	1.05	0.13	8.3
building etc. ....	20878	3096	176	14.82	0.84	5.6
sundry occupations ....		689	30			4.4
Group III .....	59289	4027	194	6.79	0.32	4.81
commodity trade .....	23216	1452	72	6.25	0.31	4.9
banking, insurance ....	2955	22	3	0.45	0.10	13.6
hotel, restaurant .....	3031	188	11	6.22	0.36	5.7
post .....	1829	44	3	2.40	0.15	6.8
telegraph, telephone....	1306	11	2	0.82	0.15	18.1
railways .....	2579	183	19	7.09	0.69	10.4
tramways .....	3022	96	5	3.17	0.16	5.2
road transport .....	8917	850	53	9.74	0.62	6.2
(chauffeurs, drivers) ..	4042	651	34	16.10	0.84±0.145	5.2
shipping .....	2881	367	26	12.73	0.90±0.176	7.1
seamen .....	925	269	20	29.08	2.16±0.48	7.4
Group IV .....	19954	491	74	2.46	0.37	15.1
defence .....	5073	64	6	1.06	0.12	9.3
municipal administration	2374	57	3	2.40	0.33	14.0
religion .....	569	27	1	4.74	0.17	3.7
teaching .....	2050	37	8	1.80	0.39	21.6
literature, art .....	3926	225	39	5.73	0.99±0.15	17.3
care of the sick etc. ....	3225	51	12	1.61	0.37	23.5



tionally high. The number of ulcer cases here is also rather high (39 cases), so the figures obtained ought to signify something. The average ulcer frequency figure for the entire material in relation to the number of workers within all groups is  $0.39 \pm 0.015$  %. The estimated difference is thus  $0.60 \pm 0.15$ . — Here, then, there must be a definite divergence. These patients consist of  $\frac{1}{3}$ rd musicians,  $\frac{1}{3}$ rd artists, architects and sculptors, and  $\frac{1}{6}$ th journalists and editors.

Among the other groups, persons included in group II, occupied in the building industry, show a high figure. These people visit the hospital frequently (14.82 %), but the occurrence of ulcer amongst them is within the average figure. The same applies to group III in respect of persons occupied as chauffeurs and seamen. It may be that, on account of the large number of visitors, the figures in the last column become relatively low, but the relation of ulcer to workers is nevertheless comparatively high.

## II. Occupational conditions of female ulcer patients.

The material comprises 312 cases of gastric ulcer and duodenal ulcer in women domiciled in Stockholm. It has been possible to arrange just over  $\frac{1}{3}$ rd of the cases in different occupational groups (table 3). The rest — barely  $\frac{2}{3}$ rd of the cases, it has not been possible to specify properly, and they have therefore been combined into two large groups — single and married women.

In 146 cases the patients were married, in 26 cases spinsters or single. Obviously this group of single women should include those comprised in the occupational groups, for only a few women in those groups were married. We obtain, then, 146 married and 141 single patients, i.e. about 50 % of each. In order to ascertain whether this corresponds to the social structure of the population, I have calculated from the Statistical Year Book the number of married and single women in the ages of 20—50 years, i.e. the years in which most cases of ulcer occur. There was however, only one table available, relating to the conditions in the cities in the year 1920, but such changes as may have occurred in the population conditions since then are probably of no significance in this connection. According to this table, in 1920, there were 210932 single and 208280 married women in the towns and cities of this country, i.e., on an average 50 % of either group. There is thus a clear agreement between the conditions in respect of population and the condi-

Table 3.

Occupational conditions of 110 female ulcer patients domiciled in Stockholm, and treated at the Serafiner Hospital during 1937—1942.

Occupations	No. of workers in Stockholm within group (a)	No. of patients at the med. polyclinic during 1937—42 (b)	No. of ulcer cases during 1937—42 (c)	b in % of a	c in % of a	c in % of b
Agriculture + subsidiary occupations .....	599	16	1	2.7	$0.16 \pm 0.16$	$6.2 \pm 6.00$
Industry and handicrafts: .....	31279	1878	19	6.0	$0.06 \pm 0.014$	$1.0 \pm 0.23$
1. Paper and printing industries .....	3814	104	3			
2. Food, beverages and tobacco industries ..	4462	73	2			
3. Textile industry ....	13436	982	13			
4. Leather and rubber industries .....	2449	176	1			
5. Unspecified industries		541	5			
Trade and communications .....	50949	2183	29	4.2	$0.06 \pm 0.011$	$1.3 \pm 0.24$
trade commodity .....	26866	1087	9			
hotels etc. ....	14800	947	16			
telegraph and telephone	3850	40	1			
transport .....	252	108	3			
Office workers in industrial and commercial groups .....	11929	730	7	6.1	$0.06 \pm 0.022$	$0.9 \pm 0.35$
Public services and the free professions .....	16489	605	7	3.6	$0.04 \pm 0.016$	$1.1 \pm 0.43$
teaching .....	4147	76	1			
care of the sick .....	7540	471	6			
Domestic work .....	30978	2668	33	8.6	$0.10 \pm 0.018$	$1.2 \pm 0.21$
Ex-workers .....	24098	889	14	3.7	$0.06 \pm 0.015$	$1.5 \pm 0.40$

tions of the present ulcer material. In this material, therefore, no predominance of either one or the other category can be found to exist.

With regard to the occupational groups, reservations must of course be made when drawing conclusions from this table, on account of the relatively small number of cases within each group. So much can be said, however, that no special occupation predominates to any extent; on the contrary, the figures obtained show a fair measure of agreement between the different groups.

### Summary.

The results of the investigation of this Stockholm material can be summarised as follows: So far as the males are concerned, gastric ulcer and duodenal ulcer have been found to occur more frequently amongst persons occupied in the building trade, amongst chauffeurs and drivers, seamen, artists, musicians, journalists and editors.

These occupations have in common a certain degree of irregularity in the mode of living. Thus, for instance, those employed in the building trade generally take their meals with them to work, and consume dry food the whole day, while persons in the other occupations specified here generally take their meals irregularly and lead a hectic and irregular lives.

In regard to the women, no certain connection between ulcer and any one particular occupation has been found to exist, (the material is, however, inadequate) or between ulcer and their civil state — married or single.

### Bibliography.

- Adler, E.: Arch. Verdgskrkh 37, 339, 1926. — Alstedt, G.: Ugeskr. f. læger 104, 1430, 1942. — Bauer, J. und Aschner, B.: Klin. Wschr. 1250, 1298, 1922. — v. Bergmann, G. und Katsch, G.: Hdb d. norm. und pathol. Physiol. III, 1159, 1927. — Cohnheim, P.: Arch. Verdgskrkh. 27, 241, 1921. — Einhorn, M.: Am. J. of med. Science. 179, 259, 1930. — Ellinger, F.: Zeitschr. klin. Med. 122, 272, 1932. — Gebhardt, F. und Richter, J.: Münch. med. Wschr. 81, 563, 1934. — Heissen, F.: Münch. med. Wschr. 209, 1921. — Kalk, H.: Neue deutsche Klin. 6, 1930. — Mattisson, K.: Das Magengeschwür. Akad. avh. Lund. 1931. — Moynihan, B.: Duodenal-såret. Sthlm. 1916. — Nicol, B.: Brit. med. J. 2: 780, 1941. — Reichert, F.: Deutsch. med. Wschr. 66, 633, 1940. — Spiegel, H.: Münch. med. Wschr. 274, 1921. — Weidinger, A.: Münch. med. Wschr. 87, 882, 1940. — Wiebel, H. und Kunstreich, W.: Münch. med. Wschr. 87, 94, 1940.
-

(From the medical clinic of Karolinska Sjukhuset, Stockholm. Chief physician: professor Nanna Svartz, M.D. and from dep. II Kommunehospitalet, Copenhagen. Chief physician: Hans Heckscher, M.D.)

## The Emphysema of the Lungs, its symptoms and relations to other diseases.

By

HANS HECKSCHER.

Submitted for publication August 2, 1944).

It is still maintained by most investigators that pulmonary emphysema is an irreparable disease caused by intrapulmonary degenerative processes. Very often the presence of emphysema in a patient is considered to be of minor importance, as the attention of the doctor first and foremost is called to other morbid changes: relapsing bronchitis, bronchial asthma or degeneration of the heart. The opinion that the pulmonary emphysema is both irreparable and negligible is, however, not in accordance with later years' observations concerning the nature of the emphysema and its relations to other diseases of the lungs and the air passages. Besides, it disagrees with the experience that such diseases, i.e. mucous affections incl. bronchitis, cardiac and respiratory neurosis and bronchial asthma, may improve due to a treatment which eliminates the dilation of the lungs. This makes necessary a renewed discussion of these problems.

### Definition and nomenclature.

In this paper and in accordance with the common terminology *emphysema of the lungs* means: a diffuse, general, «genuine» emphysema, the main clinical characteristics of which are a) distension of the lungs and b) atrophy combined with other degenerative chan-

ges of the lung-tissue. The details of its pathological anatomy are, however, so well-known that they do not need to be discussed in detail here. The classical pathologic-anatomical observations don't tell us anything with regard to the etiology and the pathogenesis of the emphysema; they may hardly be said to show more than that certain organic changes can be demonstrated in the lungs after more or less protracted illness (Tendeloo, Author). More recent investigations (Loeschke) are more significant in this respect as they have shown that the organic, atrophic processes are found exclusively in the most distended parts of the lungs, which means that the distention of the lungs is not the result of a primary atrophy and that the degenerative processes in all probability are not primary to the distension but secondary. The other forms of pulmonary emphysema, i.e. the *senile emphysema* (emphysème à petits poumons), the *local, bullous emphysema* (emphysème réticulé des tuberculeux) and the *vicarious, hyperplastic emphysema* (emphysème pulmonaire hypertrophique), are distinguished from the genuine emphysema both etiologically, pathologic-anatomically and with regard to their relations to other diseases.

To be discussed remains, however, the probability of maintaining a sharp, fundamental distinction between pulmonary emphysema and what is called «*volumen pulmonum auctum*». Regarding this question most previous investigators (Eppinger) have concluded that the term «emphysema pulmonum» is to be reserved for such cases where enlargement of the lungs are permanent and connected with atrophy and degenerative processes in the lungs, while «*volumen pulmonum auctum*» should be used characterizing cases of passing lung-dilation only, e.g. cases presenting enlargement of the lungs after acute physical exertions (Hasselbalch).

If *emphysematous patients of all sorts*, i.e. patients with incipient and uncomplicated emphysema as well as patients suffering from complicating diseases, are examined, a gradual aggravation of the health in course of time is conspicuous. A material of this kind will present a gradual passing from slight complaints to grave distress, from apparently pure functional disturbances to substantial organic lesions; generally the seriousness of the cases increases with their duration. If each individual case is considered separately it will often be possible to reconstruct its development and to discriminate between different phases which are the counterparts of the

various stages of the diverse cases composing the total material. Presumably this can mean but one thing: that in all cases uncomplicated or complicated, a common factor, viz. a purely functional disturbance, is found, which gradually gets complicated with organic changes, until the stage is reached where the latter dominate the picture. No observations deciding against this are known. (It seems extraordinarily that the following questions have not been considered seriously before: What is really the initial stage of the well-known severe and chronic cases? Could it really be possible that such severe cases with organic changes should make their appearance quite suddenly without any precursors? Might it not be more reasonable to think that the organic changes are developing gradually in connection with and resulting from functional disturbances?) In the way here described the typical cases of pulmonary emphysema with rarefaction of the lung-tissues and the other well-known anatomic changes can be traced back to merely functional disturbances. As those functional disturbances are synonymous to *»volumen pulmonum auctum»* it means that *»volumen pulmonum auctum»*, although in some cases only a transitory phenomenon, in other cases is *synonymous with the first stage of emphysema of the lungs, i.e. an incipient dysfunction disposing to perseverance and to secondary development of organic lesions*. Consequently it would be incorrect to maintain a sharp distinction between these two phenomena, all the more as a clearly defined, clinical distinguishing is impractical. The previous crucial differential diagnosticum whether the lung-borders may prove movable or not is inapplicable, as it has been demonstrated (Hofbauer, Author) that also the lung-borders in patients presenting typical pulmonary emphysema may be mobilized and normalized by breathing exercises and medical gymnastics. Besides, in a material of emphysematous patients of all sorts a transition is found from patients whose lung-borders still are mobile to patients whose lung-borders (before the treatment) seem completely fixed and displaced. Consequently the term *pulmonary emphysema* is preferable in all cases of diffuse lung-distension, whereas according to circumstances a distinction can be made between acute or chronic, uncomplicated or complicated cases.

## Physiological relations of lung-distension. Respiratory-mechanical triade under experimentally effected conditions and in emphysema.

The investigations regarding the development and especially the pathogenesis of the emphysema have not until recently had the character of direct clinical research, i.e. nosographical observations concerning the nature of the incipient emphysema. The principal part of former investigations has not — as far back as the beginning of the last century, when Laennec gave the first thorough description of the emphysema — been based upon direct observations of the initial signs of ailment but on *post mortem* observations and on speculative deductions on the basis of what had been seen in older, advanced and complicated cases (Tendeloo, Author). These two methods of research unlike in principle, one of them indirect, the other one direct, have led to quite different points of views. The previous research resulted in the dogma of the emphysema's irreparability and its occurrence in consequence of degenerative, tissue-destroying processes within the lungs. The recent research demonstrates the reversible character of the lung-distension and its automatic connection with certain anomalies in the mechanism of respiration, viz. alterations of the dynamic and the static function of the muscles of respiration. A discussion of the physiological relations of the lung-distension will clear this point.

### *Changes of the dynamics of respiration leading to changes of posture and to alterations of lung-volumina.*

Fig. 1 presents a schema of the lung-volumina during normal rest-respiration (A) and during strained respiration (B). The transition from A to B may be effected by physical exercise, by experimental stenotic breathing, by adding carbon dioxide to the respiration-air or by increasing the size of the «dead spaces» in a person who is made to breath through a tube (Haldane). The changes following this transition from A to B, from unstrained to strained respiration are fundamentally the same whether it is a question of shortness of breath in a normal person or the development of dyspnoea in a patient with insufficiency of circulation (Hofhauser). The main characteristics of these changes are under both circum-

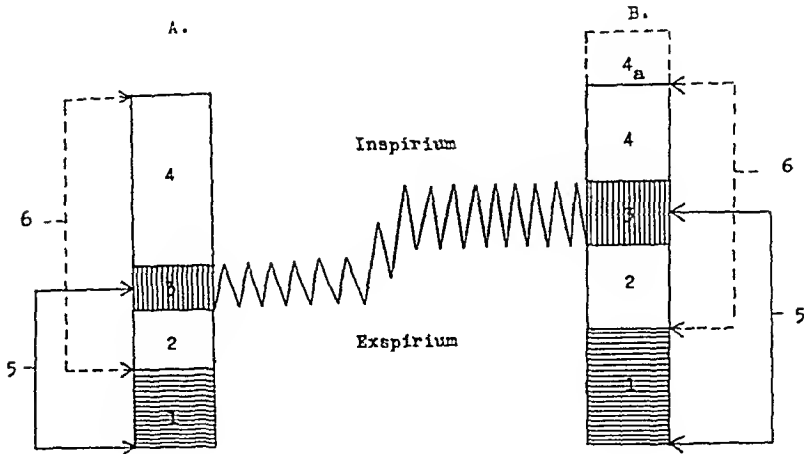


Fig. 1.

- A: lung-volumes during rest-respiration.  
 B: lung-volumes during strained respiration.  
 1: residual-air volume.  
 2: reserve-air volume.  
 3: volume of respiration.  
 4: complementary volume at disposal.  
 4<sub>a</sub>: addition to complementary volume obtained by means of extra training.  
 5: average volume of air in the lungs (indicated by the respirations mean level).  
 6: vital capacity.

stances that the depth of each breathing is increased, that both inspiration- and expiration-limit and thereby the mean respiratory level is displaced in the direction of inspirium and that the average volume of air contained in the lungs as well as the residual-air volume is increased. Simultaneously the vital capacity is decreased, so far as this decrease is not made good for by an extension of the complementary space through extra training (fig. 1: 4<sub>a</sub>). Finally, it must be maintained as a principal point *that these alterations of the different lung-volumina are identical with those known to be characteristic of the emphysema.*

But other changes in the mechanism of respiration than the alterations of the lung-volumina are involved by the passing from non-strained to strained breathing. Thus it is visible that the type of respiration changes; the abdominal type of breathing, in a subsequent chapter shown to be the normal type in women as well as in men, disappears and the breathing grows more or less thoracic when the respiration is strained, a fact which is easily observed



both in normal persons who are shortbreathed, e.g. after a run, and in dyspnoeic heart-patients. Besides, the posture is changed, what is explained by the following facts. Without further considerations it is a plain thing that changes of the type of breathing are tantamount to altered dynamic functions of the muscles of respiration. But, as these muscles in the chest-wall, in the back and in the neck are also functioning as static, i.e. posture-shaping ele-

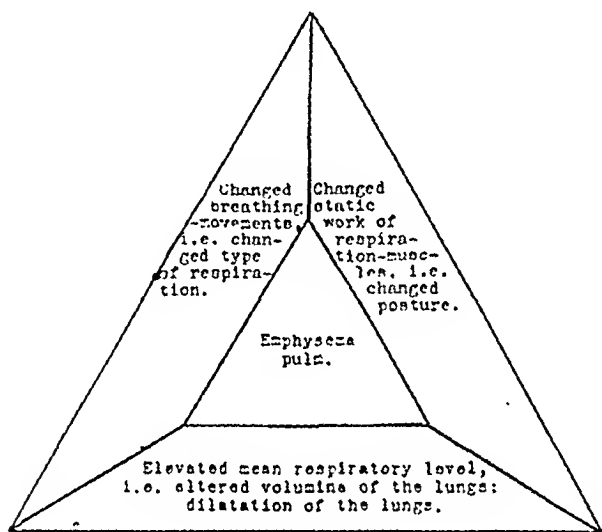


Fig. 2.

ments, a changed dynamic activity must automatically lead to a changed static activity, viz. to a changed posture — and vice versa. This may, e.g., be observed if gymnasts or runners are examined before and after their exerting performances: the shortness of breath, the thoracic breathing and the changed posture after the exertion may be equally conspicuous. (Further particulars of such posture-changes and resemblance to the habitual, postural anomalies experienced in emphysematous patients will be given in a following chapter.)

*Changes of posture leading to changes of breathing movements and to alterations of lung-volumina.*

The *triade*, a) changed movements of respiration, b) changed posture and c) altered lung-volumina, may thus be established in consequence of increased claims to the respiration; but a similar result

Table 1.  
(After Lindhard).

*Effect of some gymnastic postures upon the volumes of the lungs.*

	Vital capacity	Residual-air volume.
Standing rest-posture: .....	100%	100%
Stretch-standing posture with raised arms	90%	118%
Span-bending toe-standing posture ....	78%	125%

may be arrived at if primarily not the dynamic but the static function, the posture, is altered. This fact is evident from Lindhard's determinations of the lung-volumina in varied gymnastic postures.

It is clearly demonstrated by the figures in table 1 that the shifting from easy-standing posture to stretch-standing posture and still more the shifting to span-bending posture involves the same alterations of the lung-volumina as were induced by the transition from non-strained to strained breathing, i.e. the very same alterations of the lung-volumina which are characteristic of the emphysema. The posture settles the size and the form of the thoracic cavity — as certainly the size and the form of a room depends upon the position of the walls, the floor and the ceiling — and consequently the size and the form of the lungs. At the same time, however, the type of breathing changes, from being abdominal in easy-standing posture it grows more or less thoracic in the gymnastic postures (Lindhard). These postures are combined with a tension and flattening not only of the abdominal wall but also of the diaphragm which hampers the function of this most important respiration-muscle of the body and makes it necessary that other muscles be used. Are these gymnastic postures, however, analysed, they are found to present decisive points of resemblance to the postures automatically involved by strained breathing as well as to the habitual postural anomalies seen in some emphysematous patients (viz. the universal tightening, the elevation of the chest and the tension of the abdominal wall).

*Triade of emphysema. Experimentum crueis.*

The result of these observations is that *movements of respiration, posture and lung-volumina are automatically and most closely*

*connected phenomena*; together they form a physiological or pathophysiological *triade* which is characteristic of the pulmonary emphysema just as well as of the above-mentioned experimentally provoked conditions.

That *altered lung-volumina* are found in emphysematous patients is a well-known fact; especially the total distension, the decreased vital capacity and the increased residual-air volume are considered to be significant of the emphysema. That *mixed abdominal-thoracic* or *pure thoracic type of breathing* and *postural anomalies* are experienced in the great majority of emphysematous patients is proved by the author in previous papers, which fact concerns cases of early and uncomplicated pulmonary emphysema as well as cases of emphysema complicated with relapsing bronchitis, cardiac and respiratory neurosis or bronchial asthma. In most cases the anomalies are so conspicuous that they can be observed immediately by anybody who has his attention turned to them. (They are discussed in details in subsequent chapters of this paper.)

While of the three phenomena composing the *triade* only the alteration of the lung-volumina has been especially taken notice of by the majority of previous investigators, who ignored the change of type of breathing and the change of posture, the recent research has aimed at establishing an *experimentum crucis* by proving that normalization of movements of respiration as well as normalization of the posture can make the lungdistension disappear. Thus Hofbauer who employed special breathing-exercises, »Sunim-uebungen«, succeeded in getting the respiration of a number of emphysematous and asthmatic patients under control and in this way »nicht bloss den Husten sowie die Lungenbläehung zu bekaempfen, sondern in gleichem Ausmasse die Thoraxverschiebungen zum dauernden Verschwinden zu bringen«. Corresponding results have been obtained by the author by means of a gymnastical posture-correction in emphysematous patients of all kinds, uncomplicated as well as complicated cases. The treatment, generally carried through successfully, led after a normalization of the posture simultaneously to a normal abdominal type of breathing and to normally placed as well as normally movable lung-borders. Where special complications (e.g. bronchiectasiae, heart-disease) were not present a clinical improvement, and often a complete and lasting disappearance of all subjec-

Table 2.

(After Heckscher.)

*Primary causes of the development of emphysema: various changes in the mechanism of respiration. (Survey of 181 patients with beginning emphysema.)*

A: static changes = postural anomalies.

B: dynamic changes = altered breathing-movements.

A	A and/or B	B	Number of patients.
		Catarrh and/or bronchitis	45
	Neurosis cordis et respirationis.		27
Adipositas-posture			23
Tightened posture (soldier-posture, flat-back posture)			15
		Nasal disease with obstruction	15
		Cardiac insufficiency	12
Deformatio thoracis due to diseases of skeleton parts or joints			12
Asthenic, kypholordotic posture			6
		Tuberculosis pulmonum	5
	Hard manual labour		5
	Contusionis thoracis sequelae		3
	Incerta		13
Total			181

tive and objective symptoms followed the disappearance of the emphysema.

These investigations have decisively proved both the functional and at least to a certain degree reversible character of the pulmonary emphysema and the automatic connections between lung-distension, altered type of breathing and postural anomalies even in typical emphysematous patients.

### Etiology and pathogenesis of emphysema.

In the author's previous investigations the question of the etiology and pathogenesis of pulmonary distention was dealt with by means of examinations concerning patients suffering from emphysema *in an early stage*, i.e. patients with uncomplicated or only slightly complicated emphysema. These examinations gave as result, that the cause could not be found in previous tissue-destroying diseases of the lungs, as such diseases were ruled out in the great majority of cases, but that nearly all the cases were found originating in *functional disturbances of the mechanism of respiration*.

Table 2 shows a grouping of 181 observed cases based on the recognition of etiological factors (Author 9a, 9c). Three main groups are met with: A) cases in which anamnestic and objective examinations indicate that the pulmonary emphysema originates in primary postural anomalies, B) cases, where the pulmonary emphysema is induced by primary anomalies of the movements of breathing and, finally, A/B) cases where a combination of postural anomalies and anomalies of the movements of breathing may be active. The material studied in detail divides into sub-groups:

*Cases of pulmonary emphysema originating in mucous affections of the upper air passages and/or bronchitis. Cases of pulmonary tuberculosis.*

The decisive factor for such patients is the persistent cough itself which results in a persisting cough-readiness, i.e. a habitual accumulating of air in the lungs as a preparation for the act of coughing and therefore a habitual displacement of the mean respiratory level in the direction of inspiration: a habitual distension of the lungs.

*Cases of cardiac and respiratory neurosis.*

Conspicuous in these cases is a psychogenous («mimic») tightening of the static muscles and a contraction of the diaphragm. As on account of their greater strength and livelier innervation the muscles of inspiration are dominating compared with the muscles of expiration, the result of a common tightening is, besides the lowering of diaphragm, a change of posture, a dilation of chest and lungs and a displacement of the mean respiratory level in the direction of inspiration. An acute form of this «mimic» change of posture, combined with acute shortness of breath and in some cases even pronounced dyspnoea and difficulties of speech, is seen in persons under the spell of acute nervous agitation. In patients who for a longer time have suffered from grave nervous disturbances the changes of posture etc. often grow habitual. In these patients as in other emphysematous patients the type of breathing has changed from abdominal to thoracic. Besides, a periodically appearing *neurotic respiration* (further detailed in a following chapter) can be observed in many patients. It seems as if in some of these patients this neurotic respiration is the first observable sign of respiratory anomalies and precursory to the more permanent changes of posture and type of breathing. Thus in some of these cases dynamic changes may be primary to static changes.

*Cases of adipositas, especially adipositas abdominis, and postural anomalies due to changed balance. (v. table 9, group II B a—b.)*

In these cases the primary importance of the change of posture is obvious. The great weight of the abdomen leads to a backward leaning of the trunk which is effected by means of an augmentation of the lumbar lordosis (table 9, group II Ba) or a hyperextension of the hip-joints (table 9 group II B b). The chest is widened, especially in its lower parts, and drawn upwards to be used as a fix-point for the muscles in the chest and in the abdominal wall carrying the bulk of the abdomen. The cavity of the chest and the lungs are much enlarged frontally and sagittally; but in some of these patients a distension in the cranio-caudal diameter is missing, as the diaphragmatic eupolas keep at a strikingly high

level due to a considerable abdominal meteorism, so that in spite of the enlargement of the lungs the stethoscopically determined lung-borders are found normal: «masked», i.e. only bi-dimensional emphysema. Similar conditions are found in some patients with abdominal tumors and in some women during the last months of pregnancy.

*Cases of tightened posture. Soldier-posture and flat-back posture.*  
(v. table 9, group III B—C).

In such patients the tightening of the posture is intentional and caused by unlucky ideas of what is sound and handsome. The «straightening» of the back, the squaring of the shoulders, the thrusting-out of the chest and the tightening of the abdominal wall in soldier-posture or flat-back posture remind of the gymnastical postures examined by Lindhard. In both types the universally augmented tension of the muscles is very apparent. The simultaneous extension of the thoracic cavity in all directions and the downward dislocation of the diaphragm are resulting in an, often enormous, tri-dimensional extension of the lungs (about further details v. chapter: postural anomalies, v. also table 9—10.)

*Cases of obstructing nasal disease.*

The provoking factor is the harassing sensation of troubled respiration, due to the hampered passage of air through the nasal air passages. This by means of a reflex action leads to forced inspiration and thus to a displacement of the mean respiratory level in the direction of inspiration, i.e. to a dilation of the lungs etc. In acute form these sequences are exceedingly common in patients suffering from acute catarrhal rhinitis; here both the altered breathing-movements the changed posture and the lung-distension are easily observed. In cases with chronic, obstructing nasal affections those changes by and by grow permanent.

*Cases of working-dyspnoea. Heart-disease. Exerting manual work.* (v. table 9, group III A).

How a strained respiration, whether in heart-patients or in normal persons, leads to the establishment of the *triade* of emphy-

sema has been explained in a preceding chapter; it is an easily recognized fact that working dyspnoea in normal persons as well as in patients suffering from insufficiency of circulation is always combined with emphysema. In normal persons the distension of the lungs and the changes of breathing and of posture are synonymous to normal reactions of the mechanism of respiration and transitory, i.e. disappearing when rest is resumed; still, if the working dyspnoea is too constantly appearing, as very often it is in transport-, harbour- and slaughter-house workers or in athletes working in a wrong style, the alterations of respiration may grow permanent. Similar happenings can be seen in heart-patients in whom the emphysema comes and goes synchronous with the dyspnoea until it grows more persistent and at last permanent as the insufficiency of circulation aggravates. Besides the shortness of breath another thing may be held responsible for the development of emphysema in some cases of workman's emphysema, as here the postural changes may be caused, at any rate partly, by the strenuous work's claim to increased physical stability, to the establishment of stronger fix-points.

*Cases of osseous-articular deformation of the chest, (rachitical, spondylitic, osteomalatic, polyarthritical).*

Here of course the changes of posture viz. the deformations of the chest are the principal and primary factor.

*Cases of asthenic kypho-lordotic posture.* (v. table 9, group I a—b and II A a—b).

In such cases the primary and decisive factor in the development of emphysema is an anomaly of posture. Characteristic for such patients is a constitutional sub-standard of the skeleton parts, which are gracile, and of the muscles, which are thin, with subnormal tonus and often atrophic. In consequence the posture is hyper-relaxed, the axes of the different body-segments abnormally deviating from the vertical — with a protrusion of the abdomen's lower part and of the pelvis, with increased lumbar lordosis (table 9 group I a) or hyperextension of the hip-joints (table 9 group I b) and with an augmented dorsal kyphosis. Thorax is of slender form;



its frontal and sagital diameters are of small size though to a certain degree they are distended on account of the thoracic respiration. The principal point is, however, that the diaphragm, especially its anterior part, is permanently flattened and drawn downwards so that it partakes but little or not at all in the respiratory movements; this involves a marked distension of thoracic cavity and lungs in the cranio-caudal direction and necessitates a thoracic respiration. Thus, in these cases the emphysema is mainly one-dimensional.

#### *Cases originating in contusions of chest-wall.*

Contusions of the chest-wall followed by pains which are accentuated by every movement of the trunk are often leading to an immobilization of the chest. On account of the predominance of the inspiration-muscles this immobilization generally means a displacement in the direction of inspirium, i.e. a distension of the thoracic cavity and the lungs. It may, however, happen that the physical consequences of the contusions are complicated with a traumatic neurosis which acts in the same way as the non-traumatic neurosis described above (cardiac and respiratory neurosis) provoking a mimical change of posture, thus cooperating with the tendency to immobilization in producing an emphysema. Such cases are described by the author in a special paper (Author: 9 d).

#### *Questionable cases.*

It remains to mention that in a few cases (13 out of 181) the etiology and pathogenesis was not properly explained on account of uncertain anamnestic informations.

#### *Summary of investigations concerning the etiology and pathogenesis of emphysema.*

In the majority of cases the enlargement of the lungs in emphysematous patients is explained satisfactorily by static changes (postural anomalies) or by alterations of the breathing-movements caused either by bad habit of posture, traumatic injuries

of the chest-wall, osseous-articular deformations of the chest, cough, obstructing nasal diseases, working dyspnoea or by respiratory neurosis. To these etiological factors must be added bronchial asthma.

### Symptoms of pulmonary emphysema.

In itself the uncomplicated emphysema does not produce other subjective symptoms than some working-dyspnoea, and in most cases, where nothing else is the matter, this tendency to shortness of breath does not amount to much. The other symptoms which in the incipient stages of the disease makes the emphysematous patients ask for medical assistance are signs of complicating diseases, usually affections of the mucous membranes of the upper air passages and affections of the muscles in the chest-wall and the back. Together with *shortness of breath, cough, pains in the chest and in the back* and a *feeling of oppression* are the complaints most often met with.

Table 3.  
(After Heckseher)

*The dominating subjective symptoms in 181 patients with emphysema in the beginning stage.*

Primary etiological factor	Number of patients				
	Total	Shortness of breath	Cough	Pains in chest & back	Oppression feeling.
Catarrh and/or bronchitis . . . .	45	32	42	10	2
Neurosis cordis et respirationis	27	24	5	12	9
Adipositas posture . . . . .	23	19	9	12	5
Soldier-posture . . . . .	15	6	4	15	2
Obturator nasi . . . . .	15	15	6	6	4
Morbus cordis . . . . .	12	12	4	4	2
Deformatio thoracis . . . . .	12	12	5	5	1
Asthenic kypho-lordotic posture	6	5	2	2	2
Pulmonary tuberculosis . . . . .	5	4	5	1	2
Hard manual work . . . . .	5	5	2	3	1
Contusionis thoracis sequelae	3	3	0	3	0
Incerta . . . . .	13	7	3	7	3
Total . . . . .	181	144	90	80	33

Table 4.

*Working of the numbers given in table 3 on the basis of etiological and patogenic factors.*

Etiological/patogenic factor	Total number of patients	The frequency of the symptom in the material			
		Dyspnoea	Cough	Pains	Oppression
Primary postural anomalies (compare table 2).....	56	75%	36%	61%	18%
Cough .....	50	72%	94%	22%	8%
Obturation nasi.....	15	100%	40%	40%	27%
Working-dyspnoea .....	17	100%	35%	41%	18%
Neurosis .....	27	88%	19%	44%	33%

It appears from table 3 and 4 that *shortness of breath* is the symptom most often found in these cases. In most of the neurotic patients the dyspnoea predominantly had the character of resting-dyspnoea, whereas most other patients complained of working-dyspnoea, especially the patients suffering from cardiac insufficiency, from the consequences of hard manual work or from obstructing nasal affections. *Cough*, most naturally, was frequently found in cases where catarrh, bronchitis or tuberculosis had been the primary etiological factor. *Pains in the chest or back* (myalgiae e functione) were common in patients with primary postural anomalies (compare table 2). A *feeling of oppression* worried especially the neurotic patients. Most remarkable is, however, the fact that all these different symptoms generally were combined in patients of all kinds, as e.g. patients with primary postural anomalies by and by developed shortness of breath and cough, whereas patients primarily suffering from catarrh or bronchitis in course of time grew dyspnoeic and got myalgic pains. Thus, although every single symptom has its special origin, as e.g. cough appears from mucous affections and pains from overstrained muscles, together they form a *complex of symptoms* characteristic of and conditioned by the central factor: the emphysema.

**Successive aggravation. Development of complicating diseases. Vicious circles.**

*Emphysema and dyspnoea.*

In itself the emphysema involves a tendency to shortness of breath, this is a general clinical observation backed up by a number of patho-physiological investigations. Decisive is first and foremost that the increased average air-content of the lungs and the residual-air volume correlate with a distension of the (anatomical) injurious space and with an augmentation of the (physiological) effective dead space, syn. *volumen inefficax* (Engelhoff). The consequences of this are, as found in emphysematous patients compared with normal persons, that the inspired air is mingled unevenly with the air in the alveolar parts of the lungs (Sonne & co-operators) and that the mechanism of gas-exchange in the lungs is functioning less economically. Therefore an increase of gross-respiration is necessary in emphysematous patients in order to keep up the size of the net-respiration. Now, this increase of gross-respiration is effected partly by hastening the rate of breathing and partly, in some cases even largely, by augmenting to the depth of respiration; this involves that the respiration is displaced still more in the direction of inspiration, the average air-content of the lungs increases etc., etc. Thus a *vicious circle* is established.

Next to mention is that the share of work, both static and dynamic performed by the respiration-muscles is greater in emphysematous patients where the gross-respiration is augmented than in normal persons and more costly, because, according to the laws of physiology, every muscular contraction (and maintainance of contraction during static work) is especially exerting when in the postural anomalies the muscular fibres are contracted and shortened. Thus, in reality, *the postural changes in pulmonary emphysema are tantamount to increased physical labour*; this, of course, applies still more to the tightened soldier-, flat-back or workers-postures than to the more asthenic postures. The extra burden is especially perceptible when exercise (running, climbing stairs etc.) intensifies the demands to respiration at the same time as the respiratory reserve dwindles corresponding to the decrease of vital capacity and the complementary air volume (comp. fig. 1). The relation between emphysema and shortness of

breath is consequently reciprocal: *emphysema disposes for shortness of breath and is itself increased by shortness of breath*; evidently this means a *vicious circle*.

### *Emphysema and affections of mucous membranes in air passages.*

The existence of close connections between emphysema and catarrhes of the mucous membranes of the upper air passages and bronchitis is already emphasized by Laennec, whereas the connections between emphysema and nasal diseases tending towards nasal obstruction has been established, by French investigators too, about the century's end. The explanations offered were previously rather one-sided stressing the primacy of the mucous affections and the significance of cough to the development of emphysema. In fact, cases demonstrating the happening of things this way are often met with (v. above chapter: cases of pulmonary emphysema originating in mucous affections etc.). However, it appears from recent observations that the mucous affections in other cases are secondary to emphysema, e.g. when patients with emphysema due to soldier-posture develop rhinitis or dry catarrh followed by relapsing bronchitis. Provoking factors in such cases are presumably the exsiccation and the heavier bombardement of the membranes of the air passages with dust and microbes, due to the increased gross-ventilation, together with a diminished blood-supply of the walls of the stretched bronchii and bronchioli in the distended and bloodless lungs. This, of course, means another *vicious circle*, as such affections of the mucous membranes in producing cough will often by and by lead to enlargement and stabilization of the emphysema. *Emphysema disposes for mucous affections and mucous affections dispose for emphysema.*

### *Emphysema and myalgic pains.*

It is explained above (v. chapter: cases originating in contusions of chest-wall) how emphysema may develop after a contusion of the chest-wall, pains in the injured parts (muscles, periostium) provoking an immobilization and a distension of thorax; thus pains may be the cause of emphysema. On the other hand it is a common experience in emphysematous patients of all kinds that at one time or other they will complain of pains located to the various static muscles in the

chest wall and in the back where palpable local changes of tension and density can be demonstrated; that such *myalgiae e labore* may develop in emphysematous patients, in the muscles overstrained by static work conditioned by altered posture, is entirely in accordance with what is known about the pathology of the muscles. Thus, *muscular pains may provoke emphysema and emphysema be the cause of muscular pains: again a vicious circle.*

### *Emphysema and neurosis.*

In a preceding chapter (v. chapter: cases of cardiac and respiratory neurosis) it is made clear how a respiratory neurosis may cause the development of *emphysema* by means of a mimical tightening of the posture or by certain alterations of the breathing-movements: neurotic respiration. It is observed, however, in other groups of emphysematous patients that the different complaints caused by the emphysema: shortness of breath, muscular pains and feeling of oppression may induce or aggravate an anxiousness which takes the form of a respiratory (and cardiac) neurosis augmenting the emphysema. Thus *neurosis may cause the development of emphysema and emphysema be the cause of neurotic disturbances: a new vicious circle.*

### *Summary of observations concerning the successive aggravation of emphysema.*

Each of the phenomena: cough, nasal obstruction, cardiac and respiratory neurosis, myalgiae thoracis or shortness of breath may cause the development of emphysema or aggravate an emphysema already existing. On the other hand, whether originating in one of those factors or e.g. in an intentional soldier-posture the emphysema may invoke mucous affections, myalgic pains, shortness of breath or nervous alterations, possibly several of these complaints simultaneously.

Thus conditions may often seem rather complicated due to the possibility of various vicious circles playing a rôle, and it may be impossible to reach decisive conclusions regarding the primary etiological factor, especially in advanced cases. When, nevertheless, this could be done in the majority of cases dealt with above, the cause is undoubtedly that these were early and yet not

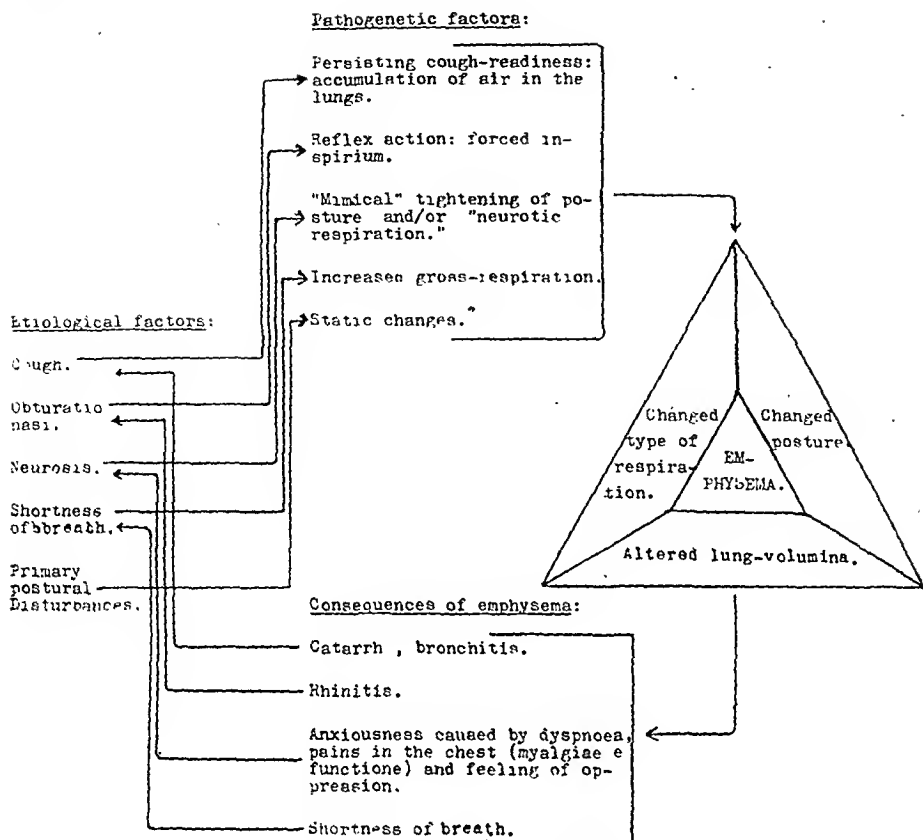


Fig. 3. Development and successive aggravation of emphysema. Vicious circles.

very complicated cases. This makes evident the advantage of studying, for the purpose of elucidating the primary etiological moment in the disease, the early cases and not the inveterate.

### Complicating diseases.

It appears from what is said above that emphysema is combined with a tendency to increased ailments and a development of complications in course of time. Such complicating diseases are first and foremost *relapsing bronchitis*, *cardiac and respiratory neurosis*, *bronchial asthma* and *insufficiency of the heart*. That the connections between emphysema and these diseases are causal and not casual emerges from the frequency of complicated cases observed in everyday's clinical work. Decisive in the same direction is the

fact, emphasized above, that the elimination of emphysema has a healing influence upon the complicating diseases.

*Bronchitis recidiva. Neurosis cordis et respirationis.*

The relations between emphysema and bronchitis, the latter in many cases being the final outcome of persisting catarrhal affections, and between emphysema and cardiac and respiratory neurosis have been accounted for in preceding chapters. A detailed study of the neurosis is given by the author in a previous paper (Author: 9 b.)

*Bronchial asthma.*

The close connections between emphysema and bronchial asthma are emphasized by many investigators. Siebeck characterizes the asthma as an acute, fourdroyant decompensated emphysema, a formula which nearly covers the author's deduction that regarded from a respiration-mechanical point of view asthma can be described as an emphysema acutely augmented by every single respiration.

By a conscientious examination emphysema is always found simultaneously with asthmatic dyspnoea, and in the great majority of cases it is also found in the intervals between the attacks (v. table 5).

Table 5.  
(After Heckscher.)  
*Emphysema in asthmatic patients.*

	Number of patients.
Emphysema during attacks of asthma but not during the intervals .....	1
Emphysema also between the attacks .....	83
Unilateral emphysema on account of scoliosis .....	1
Bilateral emphysema .....	82
Only bi-dimensional «masked» emphysema in patients with abdominal adipositas .....	3
Tri-dimensional emphysema .....	79
Total: all patients examined .....	84



Table 6.  
(After Heckscher.)

*Mucous affections of air passages in patients suffering from bronchial asthma.*

	Number of patients.
Asthma without symptoms of catarrh or bronchitis.....	4
Asthma with catarrh but without bronchitis .....	12
Catarrh prior to asthma .....	5
Catarrh simultaneously with asthma .....	3
Asthma prior to catarrh .....	4
Asthma and bronchitis (and catarrh) .....	68
Bronchitis prior to asthma .....	38
Bronchitis simultaneously with asthma .....	29
Asthma prior to bronchitis .....	1
Total: all patients examined: .....	84

The explanation of this is to some extent found in the causal relations between emphysema and mucous affections and between emphysema and respiratory neurosis and in the regular presence of such affections in asthmatic patients. As to mucous affections, numerous accounts point to the appearance of nasal diseases in the greater part of asthmatics; and investigations, e.g. those published by the author (9 c), have demonstrated the regular connection between asthma and other mucous affections in the air passages. (It must be noticed that there can be maintained no sharp distinction between catarrh and bronchitis, neither generally nor in the individual case, as e.g. the disease may begin as a dry catarrh and develop into a combination of or an alternation of catarrh and bronchitis, the latter eventually dominating.) From table 6 it is learned that the mucous affections (in Denmark) in most cases are playing an important rôle as forerunners for asthma, whereas it is comparatively rare that asthma appears before catarrh or bronchitis. Thus one seems entitled to judge that the development of asthma in the majority of cases goes along the line: mucous affections → emphysema → asthma, or: emphysema → mucous affections → asthma. That mucous affections often will have allergic character, does not seem to be of special significance in this connection.

In most asthmatic patients neurotic alterations are rather conspicuous, this is a general observation; besides, it is proved by certain observations. Significant in this respect is especially the neurotic respiration often experienced in patients with asthma bronchiale. Thus, in some cases it may be observed that the patients have been suffering from typical respiratory neurosis for a shorter or longer time prior to the asthma, whereas in other cases the neurotic respiration appears in the intervals between the attacks of asthma alternating with these; finally, patients are seen whose attacks of asthma regularly and conspicuously are initiated by a shifting from normal to neurotic respiration and a transition from the latter to actual asthmatic, expiratory dyspnoea, the neurotic unevenness of breathing growing by and by more pronounced, the expirations growing more and more difficult and prolonged until each expiration is typically strained and wheezing. Such *alternation between neurotic respiration and asthma* was very conspicuous in 11 out of 84 asthmatic patients observed by the author, and was found, although less pronounced, in numerous other patients. Therefore, in consequence of the above-mentioned causal relations between respiratory neurosis and emphysema, it seems well founded to state that the development of asthma in some cases goes through the stages: neurosis  $\rightarrow$  emphysema  $\rightarrow$  asthma or: emphysema  $\rightarrow$  neurosis  $\rightarrow$  asthma.

#### *Disease of the heart.*

The connections between emphysema and cardiac disease may be named reciprocal too, although in most cases (v. chapter: cases of working dyspnoea etc.) the cardiac disease is the primary factor and the emphysema a consequence of the working dyspnoea caused by the cardiac insufficiency; a development of that kind is not at all unusual, dyspnoea leads to emphysema. On the other hand it is a common experience that emphysema, catarrh, bronchitis (maybe bronchiectasiae and subsequent infections) in course of time may wear out the heart and result in a degeneration of the myocardium, a sequence of things involving another vicious circle. Finally must be mentioned the not altogether rare cases of *cardiac asthma bronchiale* described by the author (9 c) (7 out of a series of 150 cases of bronchial asthma treated in the

municipal hospital in Copenhagen in a certain period of time) were characterized by a rather sudden development of cardiac insufficiency, pulmonal hypostasis and typical bronchial asthma besides by a prognosis mala quoad tempus. Very often these patients have never before presented symptoms of heart-disease or asthma; the rapid and malignant course of the disease distinguishes them from the great majority of asthmatics. Here, too, the emphysema is conspicuous.

### Particulars of objective cardinal symptoms of emphysema.

#### *Changed type of breathing.*

According to the traditional conception the type of respiration is different in men and in women, as the abdominal type is said to be normal in men, the thoracic in women (and children). The investigators responsible for this conception have not, however, taken into consideration neither the double, i.e. dynamic and static, function of the respiration-muscles, which makes the type of breathing depend upon the posture, nor the fact that the posture and hence the respiration can be influenced by psychic factors. Thus it is often seen that the posture is tightened considerably when during a medical examination the patient or the person to be examined tries to look his best, and that simultaneously the type of breathing changes from abdominal to thoracic. According to the experiences of the author this way of reacting is still more common in women than in men. Finally, it has to some extent been ignored that tight-fitting clothes (corsets etc.) are the cause of altered posture and changed type of breathing in many women.

As detailed in another paper (9c) the author's examination of 1200 young and healthy probatory nurses gave as result that the type of breathing (in habitual standing posture) was abdominal in 90 % but more or less thoracic in those 10 % who presented a soldier-posture or certain other postural or structural faults. It must therefore be maintained that the normal type of breathing both in men and in women is the abdominal, nota bene in normal standing posture.

If the person examined changes his posture the type of respiration is changed too according to the changed static conditions, although the normal person during all variations of position

uses as much as possible the diaphragmatical (abdominal) respiration, because this is the least costly. Thus an abdominal breathing is seen in all relaxed positions; but in any position, even restpositions, connected with certain postural anomalies the type of breathing is changed as seen in many emphysematous and asthmatic patients, who even in sitting or lying positions present a thoracic respiration. The detailed study of these phenomena in each individual case is of importance, as the therapeutic measures against the emphysema must be based upon a thoroughly normalization of the posture — and the breathing — in all positions. In order to simplify the account of these problems it is, however, practical to subject only the observations regarding the standing position to a special report, as it is possible to make observations and to arrive at conclusions also regarding other positions from what is learned in this way.

Thus, in normal persons standing at rest the breathing is abdominal, but when the posture is tightened (e.g. in stretch-standing position) and the diaphragm is contracted and lowered, or when the respiration is strained because of physical exercise the thoracic, auxiliary respiratory forces are taken into use in increasing degree.

Table 7.

*Types of breathing (in easy-standing posture), schematically.*

<p><i>Normal.</i></p> <p><i>Even, i.e. of regular rhythm and with excursions approximately equal in size.</i></p>	<p><i>Abnormal.</i></p> <p><i>More or less uneven, i.e. of less regular rhythm and with excursions of varying size; in some cases "neurotic respiration".</i></p>
<p>1) abdominal (*primarily abdominal*).</p>	<p>2) mingled abdominal-thoracic.</p> <ul style="list-style-type: none"> <li>a) low-costal.</li> <li>b) dorsal, syn. flank-respiration.</li> <li>c) high-costal.</li> <li>d) en cuirasse respiration.</li> <li>e) asynclronous.</li> <li>f) asynclronous paradoxical.</li> <li>g) paradoxical.</li> </ul> <p>3) thoracic.</p> <ul style="list-style-type: none"> <li>a) en cuirasse respiration.</li> <li>b) high-costal.</li> </ul> <p>4) *secondarily abdominal*.</p>

This is observed in normal persons, but a similar transition takes place in emphysematous patients, when the disease by and by aggravates, leading from abdominal through mingled abdominal-thoracic to exclusively thoracic breathing. A development of that kind demonstrates an aggravation of the illness and an increasing limitation of respiratory reserve. If it goes on, the type of breathing may ultimately be seen to change again, this time in the reversed direction, from thoracic to abdominal (*secondary abdominal*) type. This fact is observed in highly dyspnoeic patients when the auxiliary muscles are so extensively contracted that the outmost limit of thoracic inspiration has been reached. The thoracic respiration is hereby exhausted, cannot yield more, and in order to keep things going the organism must recur to a diaphragmatical breathing. During improvements a succession of backward changes may be experienced, i.e. a return from «secondary abdominal» type of breathing to thoracic and from this further on to normal abdominal respiration. Simultaneously the posture and the lung-volumes will change according to the law of the *triade*.

Some words must be said about certain other, anomalies of breathing. The *en cuirasse respiration*, characteristic through massive movements of all parts of the chest as a whole, is especially observed in emphysematous patients with ball- or barrelshaped, enlarged and stiffened thoraces. The *dorsal respiration*, syn. *flank-respiration*, where the breathing-movements of the lower, dorsal parts of the chest are especially pronounced, is often seen in patients with hyperextension in the hip-joints. This anomaly often involves extra trouble, as it may prove more difficult to correct than several of the other anomalies. The *paradoxical respiration* consists in abdominal breathing-movements synchronized with the thoracic movements but reversed in direction as the diaphragm is sucked up and the epigastrium is drawn in during the inspirium. This paradoxical respiration is usually tantamount to a strong dyspnoea already of long duration. In certain cases the abdominal and thoracic movements are *asynchronous*, the abdominal movement usually starting before the thoracic. In some cases an initial and normal abdominal movement is succeeded by a reverse movement (inward-drawing of the epigastrium during inspiration) at the same time as the inspiratory thoracic movement appears; this *asynchronous, paradoxical*

*respiration* may be seen as a transitory link between paradoxical respiration and a less strained breathing.

As long as the claims to the respiration remain constant the normal breathing is nearly *even*, i.e. its excursions are approximately equal in size and rhythmical. This evenness is less pronounced in the mentioned abnormal types of respiration, where irregularities of the rhythm and of the depth of breathing are usually and generally increasing with the dyspnoea. Extreme in this respect is the *neurotic respiration* described in detail previously (Author: 9 b and 9 c). Its sporadic forced inspirations are provoked by a feeling of oppression, an intermittent feeling of air-hunger, which is very characteristic of the respiratory neurosis. (There is an obvious difference between this neurotic respiration and *Cheyne-Stokes' respiration*, whose origin and mechanism are of quite another sort; still it may be mentioned that the strained respiration during the periods of agitation belonging to Cheyne-Stokes' respiration quite regularly gives emphysema (usually transitory) in the same way as does other forms of strained respiration, e.g. the strained respiration observed in patients in diabetic or uraemic coma or in patients during surgical narcosis.)

These abnormal types of breathing are worth being taken notice of as they are significative to dysfunctions of the organs of respiration, just as irregularities of pulse are significative to cardiac dysfunctions. *An abnormal type of breathing is always tantamount to some postural anomaly and to alterations of the lung-volumes; a mixed abdominal-thoracic or an exclusively thoracic breathing in a person standing at rest is a symptom of emphysema.*

#### *Postural anomalies.*

The normal posture and the various for the emphysematous patients characteristic postural anomalies have been described in details in the author's previous papers (v., e.g., »Emphysema of the lungs etc.» Copenhagen, 1942, p. 36—40). Table 8 illustrates the relative frequency of these postural anomalies in patients suffering from emphysema complicated with cardiac and respiratory neurosis or with bronchial asthma. The relative predominance of tightened and stiffened postures in grown-up patients suffering from these diseases is found already in patients with uncomplicated

Table 8.  
(After Heckscher.)

*Postural anomalies observed in 106 patients suffering from emphysema combined with cardiac and respiratory neurosis and in 84 patients with emphysema and asthma bronchiale.*

	Neurotic patients.		Asthmatic patients.	
	Number	%	Number	%
Total .....	106	100	84	100
Tightened or partly tightened posture ....	76	72	51	61
a) with increased lumbar lordosis ..	74	70	45	54
b) with decreased lumbar lordosis....	2	2	6	7
Relaxed, asthenic posture .....	3	3	9	11
Adipositas-posture .....	15	14	9	11
Scoliosis with uni-lateral emphysema ....	3	3	2	2
Workman's S-back and barrel-shaped chest	4	4	13	15
Only intermittent postural anomaly ....	5	5	0	0

emphysema. The hyperrelaxed, asthenic kypho-lordotic posture is often seen in children and young persons with asthma. It must, however, be remembered that because of individual differences in bodily structure and in conditions of nutrition and muscular training and because of individually varied postural details all sorts of combinations may be observed. An analysis of the *types* of postural anomalies seen in emphysematous patients is given in table 9.

What is said above regarding the clinical importance of abnormal types of breathing also holds true regarding the *postural anomalies*: they are tantamount to alterations of the lung-volumes and of the breathing-movements. A postural anomaly, which causes a distension of the chest and/or a lowering of the diaphragm, is a symptom of emphysema.

#### *Altered volumina of the lungs.*

The general enlargement of the lungs is most easily proved by a stethoscopical examination demonstrating the resounding

note of percussion and the displacement of the lung-borders. That the stethoscopical examination must be carried out with the patient in *habitual* standing posture is obvious from what is maintained above; the posture must be controlled during the whole examination, as the purpose of the examination is to establish the *habitual* conditions of respiration and lungs. It is important that the percussion is not too strong or the stroke too lingering; a light and short percussion (and a plessimeter-finger closely applied to the chest-wall) is technically better fitted for the exact determination of the lung-borders and the character of the resounding note, and a heavy percussion may very well by means of a reflex action provoke a passing lowering of the diaphragm and the lung-borders in the same manner as may do other mechanical stimuli acting upon the surface of the chest (H. I. Bing).

The close supervision of the patient's posture is necessary in the roentgenological examination too, as there is no substantial difference between the X-ray-picture of a normal person in tightened and stretched posture and the X-ray-picture of an emphysematous person with soldier-posture. Further it is advisable to take the photo when the patient keeps his breath in or near the habitual mean respiratory level and not during forced inspiration when the differences between the normal person and the emphysematous patient may be effaced. Are those rules acted upon, then the expanded contours of the chest, the horizontally placed ribs, the broad intercostal spaces, the highly translucent lungs and the lowered, even during forced respiration only slightly moved diaphragm are the signs of an emphysema.

The physiological methods used in determining the vital capacity, the residual-air volume, the increased effective dead space and the uneven mixing of gases in the lungs may present a valuable supplement to the other clinical observations, perhaps mostly when by means of such methods the changes in the state of the individual patient, e.g. in consequence of therapeutical measures, may be recorded in figures.

It has been made clear above that the size of the lungs is closely dependant upon the form and the degree of postural anomaly, table 10 gives a schematic presentment of this subject.



Table  
Types of postural anomalies common in

Types of postural anomalies.		General condition of static muscles.	Position of hip joints.	Pelvic inclination <sup>1</sup>	Lumbar lordosis		
Main groups	Sub-groups				Extension	Degree	Shape
I: hyperrelaxed, asthenic.	a kypho-lordotic	lax	normal	normal	increased or normal	increased	long and slightly curved
	b mannequin- posture	lax	hyperex- tended	decreased	normal or decreased	decreased	slightly curved or flat
II: partly tightened	A: aggravated kypho-lordo- tic or mannequin- posture	a	partly tigh- tened	normal	normal	increased or normal	arched
		b	partly tigh- tened	hyperex- tended	decreased	normal or decreased	slightly curved or flat
	B: adipositas- posture	a	partly tigh- tened	normal	normal	increased or normal decreased	arched or angu- lar
		b	partly tigh- tened	hyperex- tended	decreased	normal or decreased	slightly curved or flat
III: tightened	A: workman's S-back	tightened	normal	normal	increased or normal	increased	arched
	B: soldier-posture	tightened	normal	normal	increased or normal	increased or normal	arched
	C: flat-back posture	tightenet	normal or hype- extended	normal or decreased	decreased	diminuti- ve	flat

<sup>1</sup> Angle between conjugata anatomica and horizontal line.

9. *emphysematous patients (schematically).*

Dorsal kyphosis			Abdominal wall			Depicement of shoulders		Thorax	Diste of tho		
Exten- sion	Degree	Shape	Tension of muscles	Epi- gastrium	Lower part of	Upwards	Backwards	Elevation	Shape	Frontal	Sagotal
increased or normal or decreased	increased	arched	decreased	sucked in	bulging flaccid	÷	÷	(+) <sup>2</sup>	long, narrow, flat	(+) <sup>2</sup>	(+)
increased or normal or decreased	increased	arched	decreased	sucked in	bulging flaccid	÷	÷	(+) <sup>2</sup>	long, narrow, flat	(+) <sup>2</sup>	(+)
increased or normal	increased	arched	normal or decreased	in some pa- tients suck- ed in	bulging, flaccid	÷	÷	÷	varying	÷	÷
increased or normal	increased	arched	normal or decreased	in some pa- tients suck- ed in	bulging, flaccid	÷	÷	÷	varying	÷	÷
increased	increased	arched	passively stretched muscles	bulging, distended		÷	÷	÷	extended, espcially in lower parts	÷	÷
increased	increased	arched	passively stretched muscles	bulging, distended		÷	÷	÷	extended, especially in lower parts	÷	÷
increased	increased	arched	increased	flat or drawn in	flat	÷	÷	÷	barrel- or ball-shape	÷	÷
normal or decreased	normal or decreased	arched or flat	increased	flat or drawn in	flat	÷	÷	÷	varying	÷	÷
decreased	decreased	flat	increased	flat or drawn in	flat	÷	÷	÷	varying	÷	÷

<sup>2</sup>(+) indicates that the elevation and distension of the chest in frontal and sagital directions are not permanent, as it is only caused by the thoracic respiration; it therefore disappears at the end of expiration. In all the other groups it is permanent, although, of course, varying in degree with the thoracic movements of breathing.

<sup>3</sup> In some of these patients the emphysema is only bi-dimensional, «masked» (v. text).

Table 10.

*Various anomalies of posture and emphysema.*

Dilation of thoracic cavity and lungs.	Dimension.	Prototype.	Table 9 group
1-dimensional	Cranio-caudal	Asthenic kypho-lordotic posture	I
2-dimensional, »masked emphysema»	Sagittal and frontal	Adipositas-posture with the diaphragm in a high position.	II B
3-dimensional	Sagittal and frontal and cranio-caudal	Tightened postures: soldier-posture and flat-back posture.	III

### Treatment and prophylaxis

As gradual aggravation and complicating diseases are threatening in a great many cases of pulmonary emphysema, it is a matter of importance that the right treatment is instituted at an early stage. This treatment must be based both upon an elimination of the primary etiological factor (the intentional tightening of the posture, the cough-provoking mucous affection, the cardiac insufficiency etc.), where this is possible, and upon the direct treatment of the emphysema by means of posture- and breathing-correcting measures. Normalization of the breathing-movements can be effected in the way of Hofbauer by using special breathing-exercises, whereas a normalization of the posture is carried through by means of medical gymnastics described by the author (9 c). These methods can often be combined advantageously, although in most cases the posture-correcting treatment appears easiest and most efficient; they are discussed in detail in the author's previous papers (most thoroughly in »Emphysema of the lungs etc.» Copenhagen 1942, p. 45—62).

By breathing-exercises it is sometimes possible to change the type of breathing from abnormal to normal, from thoracic to abdominal without effecting a change of posture; but then the bettering of the state it is not dependable, and relapses are likely to come. This is experienced in some patients who learn to concentrate on abdominal breathing; they may be able to perform this abdominal breathing intentionally, but it doesn't grow a habit,

and very little is gained. The posture-correcting treatment is a surer way to simultaneous normalization of posture and breathing than are breathing exercises.

If the patients are attended to at a rather early stage, before the development of peribronchitis or bronchiectasiae has taken place and before the heart is worn out, it will be possible in the majority of cases to eliminate the emphysema, to break the *vicious circles*, and to ensure an improvement of the state of health as a whole. This is experienced not only in cases of uncomplicated emphysema but also in cases complicated with relapsing bronchitis, neurosis or bronchial asthma; in most such cases a treatment carried through along these lines will involve recovery, as in this way those complicating diseases are being given a *causal treatment*.

It is equally important that the question of prophylaxis is kept present, and that parents, teachers and instructors in athletics and in military drill are taught the importance of a normal bodily posture. Although a certain improvement has been reached in this respect during the last 10—20 years, among other things due to the effect of modern theories of gymnastics (Lindhard), it is still desirable to reduce the persisting influence of the previous postural ideal, the stiffened soldier-posture, and to teach all people the advantages of a normal posture. In this way we certainly should succeed in diminishing the number of emphysematous patients.

### Conclusions.

Changed type of breathing, change of posture and altered lung-volumina are three automatically connected phenomena building together a physiological respectively patho-physiological *triade*. This *triade* is established in normal persons when the respiration is strained or when the posture changes in certain ways. Under such circumstances these changes in the mechanism of respiration are only passing; but in emphysematous patients this triade persists, the changes of breathing-type and posture establishing together with the alterations of the lung-volumina the objective, cardinal symptoms of emphysema. Still here, too, totally normal conditions can be reestablished by a treatment which normalizes the posture and the breathing-movements and which normalizes

at the same time the size of the lungs, the vital capacity and the residual-air volume. Essential in this treatment is posture-correcting medical gymnastics possibly combined with special breathing-exercises.

Neither a systematic nor a clinically feasible distinction is found between emphysema and »*volumen pulmonum auctum*», the latter being identical with the beginning stage of emphysema.

The etiological basis of the emphysema is in most patients either cough-involving affections of the mucous membranes of the air passages, nasal diseases with obturation, cardiac diseases or hard manual work giving working dyspnoea, respiratory neurosis or habitual postural anomalies.

The pathogenetic active factor is either changes of static nature, i.e. postural changes, or dynamic changes, i.e. changes of breathing-movements.

The symptoms most frequently observed in emphysematous patients are, besides the three cardinal symptoms mentioned above: shortness of breath (dyspnoea), cough, pains in the chest and back and oppression, these symptoms building together a complex of symptoms characteristic of the emphysema. These complaints may in some cases originate in a disease prior to the emphysema, e.g. mucous affections, respiratory neurosis or cardiac insufficiency; but in other cases the emphysema is the cause of their appearance, as the emphysema itself disposes to a forthcoming of secondary ailments: shortness of breath (more costly respiration), cough (secondary mucous affections), pains in the chest and back (myalgiae e functione) and oppression (increased tightening of diaphragma). In this way various vicious circles may be acting, the result being a gradual aggravation of the illness and the appearance of relapsing bronchitis, cardiac and respiratory neurosis, bronchial asthma and in some cases finally degeneration of the heart.

A survey is given of the abnormal types of respiration seen in emphysematous patients and of the different postural anomalies causing a dilation of the lungs in the frontal, sagital and cranio-caudal diameters.

Finally the question of treatment and prophylaxis is touched upon.

## Literature.

1. Anthony, A. J.: Funktionsprüfungen des Atems, Leipzig 1937. —
  2. Bohr, Chr.: Deutsches Arch. f. klin. Med.: 88: 385, 1907. — 3. Cousteau: Rôle de l'obstruction des fosses nasales dans la pathogénie de l'emphysème pulmonaire. Paris 1899. — 4. Dietrich, R.: Die Atembewegungen der Norm und Fehlform. Stuttgart, 1937. — 5. Donay, E.: Le thorax et l'emphysème. — 6. Enghoff, H.: Skand. Arch. f. Physiol.: 63: 15, 1931. — 7. Eppinger, H.: Prag. Viert. f. prakt. Heilk.: 132: 4, 1876. — 8. Faust, J.: Aktive Entspannungs-Behandlung. Stuttgart-Leipzig, 1936. — 9. Heckscher, H.: a) Acta med. scand. suppl. LXXVIII: 469, 1936. — b) Acta med. scand.: 99: 162, 1939. — c) Emphysema of the lungs and its significance to relapsing bronchitis, cardiac and respiratory neurosis and bronchial asthma. Copenhagen, Munksgaard 1942. — d) Acta med. scand. 120: 53, 1945. — 10. Helweg, J.: Om Funktionsmyopathien som smerteårsag. København, 1934. — 11. Herz, M.: Die sexuelle psychogene Herzneurose. Wien-Leipzig 1909. — 12. Hofbauer, L.: a) Atnungspathologie u. -therapie. Berlin 1921. — b) Handb. d. norm. u. path. Physiol. II: 373. Berlin, 1925. — 13. Laennec, R. T. H.: Traité de l'auscultation. 4<sup>e</sup> edit. Paris, 1837. I. — 14. Lindhard, J.: Skand. Arch. f. Physiol. 47: 188, 1926. — 15. Loeschke, H.: Henke & Lubarsch: Handb. d. spez. Anat. III/I. — 16. Roelsen, E.: a) Fraktioneret Alveoleluftanalyse. København 1937. — b) Acta med. scand. suppl. CXXIII. 1941. — 17. Tendeloo, N. Ph.: Studien über d. Entsteh. u. Verl. d. Lungenkrlh. München, 1931.
-

From Skive County and Municipal Hospital, Denmark. (Physician in Chief:  
Doctor Skat Baastrup).

## Leptospirosis Sejroe.

A Clinical Survey Based on 29 Cases.

By

OLE P. NIELSEN and ERIK HERTEL.

(Submitted for publication November 16, 1944).

---

### *Introduction.*

In 1939 Borg Petersen and Ingemann Christensen reported that in 1937 they had succeeded in isolating and cultivating an entirely new strain of leptospira, which was given the name of leptospira sejroe, as it was originally found in the blood of a patient from Sejro.

During the past 6 years cases of disease caused by this or closely related forms have been diagnosed with increasing frequency in this country, some of these cases having been published as casuistic reports. No larger publication on diseases due to leptospira sejroe or to closely related forms has as yet appeared, for which reason a report will be given of observations and experiences regarding 29 cases, which during the years from 1937—43 have been admitted to and treated in the medical department of Skive Hospital, 23 of them having occurred in the course of the last year.

### *Bacteriology.*

The bacteriological investigation of the cases has been made by The State Serum Institute. In 9 cases leptospirae from the blood

have been cultivated (citrate blood taken under sterile conditions). The cultivation has taken place on the day of admission or the day after; that is in our cases 2—7 days after onset of the illness. In 8 cases the leptospira sejroe was demonstrated, in 1 case the leptospira saxkoebing. As for the rest of the patients the diagnosis was made serologically, that is by means of positive sero-reaction with leptospira sejroe and eventually also with leptospira saxkoebing. In 26 cases the reaction was found to be positive in the dilution 1: 3000 of the serum or more, a fact, which may be considered conclusive of acute leptospirosis, provided that the clinical picture does not tell against this diagnosis. In 3 cases the titre was only 1: 1000, but in 1 of these the leptospira saxkoebing was grown from the blood, and in the remaining 2 cases the clinical picture and the course of the illness were typical of the disease. The low titre in these 3 cases is undoubtedly due to the comparatively early stage at which the blood sample was taken, namely already on the 9th and 10th day of disease, almost the earliest stage, at which a positive result of a serological investigation may justly be expected.

A comparison between the different titre-values in the different patients tends to show that the sero-reaction very often is equally pronounced for the leptospira sejroe and the leptospira saxkoebing. We have inquired at The State Serum Institute, (Dr. Borg Petersen) whether, in cases like that, it is possible to decide which of the 2 forms has given rise to the disease, and the answer was in the negative. The institution further informs that experiments of absorption, which have been made on such sera in order, if possible, to settle this question, reveal that in addition to the leptospira sejroe and saxkoebing there is most probably found still another form in this country closely related to the 2 already known. However, this «third form» has not yet been identified. Dr. Borg Petersen has made experiments of absorption regarding 9 patients, and in 4 of these the disease was most likely due to an infection with the «third form». Presumably only 3 of them were infected with leptospira sejroe, as in these cases it was possible to remove all of the antibody by means of the leptospira sejroe. In 2 cases no safe conclusions could be formed from the result of the experiment of absorption.

Only one of our patients had jaundice, and in this case the infection was apparently due to the «third form»; the other 3 cases be-



longing to the »third form» did not in any respect differ clinically from unmistakable cases of infection with leptospira sejroe, and at present it must be admitted that no method is known, by which the cases may be grouped clinically according to their types. Consequently in our material we have chosen to include them in one single group as leptospiroses of the sejroe group.

In 4 cases leptospirae have been looked for in the urine. Leptospirae are found here on about the 21st day of disease; but as most of the patients have been dismissed at that time these investigations have not been carried out with consistency. A positive result has been obtained only in 1 of 4 cases.

### *Epidemiology.*

Recent investigations (Borg Petersen, Mino in Italy) tend to show that mice play an all-important part as a source of infection in case of several forms of leptospira. Our observations point decidedly in the same direction.

In February 1939 Dr. Borg Petersen succeeded for the first time in growing a strain of leptospira of the sejroe group from the kidney of a mouse, caught in the pantry of a farm in Vejby in Salling. At that time the maid from the farm was lying in the department suffering from a leptospirosis. According to the statement of the patient there were many mice in the pantry, and it was possible for the mice to come into contact with the food in the pantry. In still another case some mice had been caught in the pantry, and also here there were found leptospirae of the sejroe group in the mouse.

When asked, by far the majority of the patients could tell that there were mice on the premises. From a single farm 2 patients with leptospirosis were admitted to the hospital during one month, and according to the statement of the cook the kitchen and pantry of the farm swarmed with mice.

In many cases the patients maintained that there were no rats in their homes.

Mice are found much more frequently in the habitations in the country than in the flats in the towns, especially in autumn, when the mice take shelter in the houses.

Of the 29 patients 28 were from the country, only 1 patient was

## Literature.

1. Anthony, A. J.: Funktionsprüfungen des Atems, Leipzig 1937. —
  2. Bohr, Chr.: Deutsches Arch. f. klin. Med.: 88: 385, 1907. — 3. Cousteau: Rôle de l'obstruction des fosses nasales dans la pathogénie de l'emphyème pulmonaire. Paris 1899. — 4. Dietrich, R.: Die Atembewegungen der Norm und Fehlform. Stuttgart, 1937. — 5. Douay, E.: Le thorax et l'emphyseme. — 6. Enghoff, H.: Skand. Arch. f. Physiol.: 63: 15, 1931. — 7. Eppinger, H.: Prag. Viert. f. prakt. Heilk.: 132: 4, 1876. — 8. Faust, J.: Aktive Entspannungs-Behandlung. Stuttgart-Leipzig, 1936. — 9. Heckscher, H.: a) Acta med. scand. suppl. LXXVIII: 469, 1936. — b) Acta med. scand.: 99: 162, 1939. — c) Emphysema of the lungs and its significance to relapsing bronchitis, cardiac and respiratory neurosis and bronchial asthma. Copenhagen, Munksgaard 1942. — d) Acta med. scand. 120: 53, 1945. — 10. Helweg, J.: Om Funktionsmyopathien som smerlesarrag. København, 1934. — 11. Herz, M.: Die sexuelle psychogene Herzneurose. Wien-Leipzig 1909. — 12. Hoffbauer, L.: a) Atmungs-pathologie u. -therapie. Berlin 1921. — b) Handb. d. norm. u. path. Physiol. II: 373. Berlin, 1925. — 13. Laennec, R. T. H.: Traité de l'auscultation. 4<sup>e</sup> edit. Paris, 1837. I. — 14. Lindhard, J.: Skand. Arch. f. Physiol. 47: 188, 1926. — 15. Lörsche, H.: Henke & Lubarsch: Handb. d. spez. Anat. III/I. — 16. Roelsen, E.: a) Fraktioneret Alveoleluftanalyse. København 1937. — b) Acta med. scand. suppl. CXXIII. 1941. — 17. Tendeloo, N. Ph.: Studien über d. Entsteh. u. Verl. d. Lungenkrh. München, 1931.
-

dition of the parenchymatous organs is the dominant feature and 3. the stage of convalescence. In the majority of our patients the toxic stage was of a very short duration, and only in few of them there was found an affection of the parenchymatous organs. Most of the patients passed quickly from the febrile period into the stage of convalescence, that in return was rather protracted in comparison to the febrile period. Most of the cases, however, were dismissed from the hospital on the 13th—20th day of disease, only some few of them lasted considerably longer, the stay in the hospital being on an average of 23 days' duration.

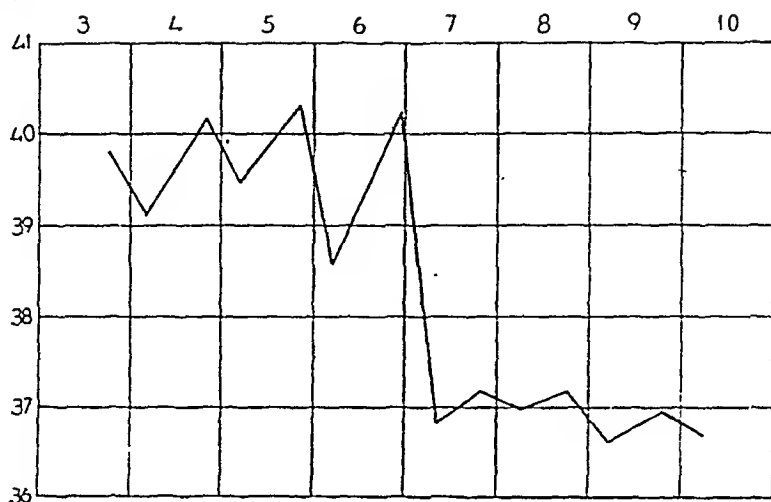
The disease is an acute infection with only few initial symptoms, which, when occurring, consist in indisposition, a little head-ache, perhaps dizziness for a couple of days previous to the onset of the disease. But most of our patients informed that the disease began quite suddenly with a pronounced feeling of illness and a rise of temperature to about  $40^{\circ}$ , sometimes up to  $41^{\circ}$  during one or two days.

*Appearance:* On admission the patients were highly febrile and slightly flushed; they were often lying with half-closed eyes, were somewhat distant, but without being able to find rest, and during the first nights they were troubled with sleeplessness.

*Temperature:* As a rule the high temperature persisted until towards the 9th or 10th day of the disease. The aspect of the temperature curve varied much from one case to another; already in 1894 F. Müller called attention to this fact in his account of an epidemic of the German Feldfieber. At the same time he pointed out that after all nearly all the temperature curves might be included under one of 3 groups, representing the following 3 types: type I with a high level for 5 to 8 days, followed by a critical drop of temperature, type II with a high level for 3 to 5 days, followed by a lytic drop of temperature and finally type III with a high level for 4 to 7 days, then a drop of temperature to normal, but 24 hours later once more rise of temperature, however at most of 1—2 days' duration. Most of the temperature curves of our patients might be included under one of these three groups. In the following the course of the temperature curve in 3 cases, demonstrating the 3 types, will be shown.

In 4 of the patients the curves of temperature corresponded to type I, in 13 to type II and in 7 to type III. In 2 cases an additio-

Day of disease



Type I.

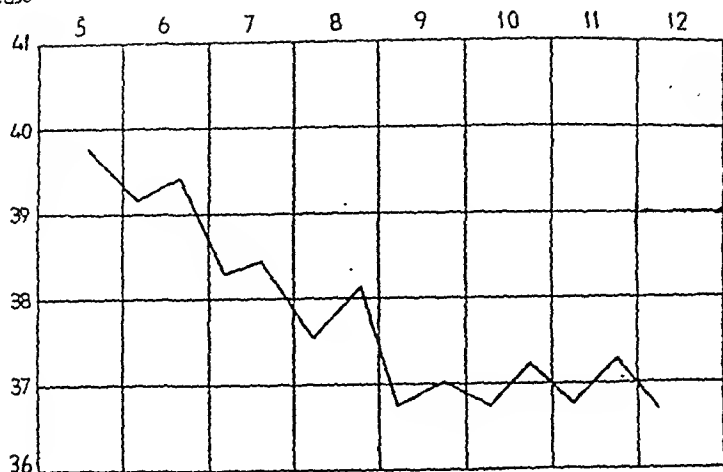
nal secondary rise of temperature occurred in the 3rd week of disease, this rise being only slight, at most to 38.2.

*Shivering Fits:* Shivering fits were present in 16 cases (59 %). In some cases the symptom was only present a single time at the beginning of the disease, while other patients had repeated shivering fits, thus one patient 9 times during the first 6 days of disease.

*Cerebral symptoms:* The most important symptom besides the rise of temperature was headache, this symptom being present in the aggregate 29 cases. As a rule the head-ache occurred from the onset of the disease, but in some few cases not until some days later. Generally the head-ache was very violent, localized in 27 cases to the forehead, in 2 cases to the back of the head. It was characteristic of this head-ache that, in the attempt of sitting up, the pain was markedly aggravated, much more than this is the case in other febrile diseases, indeed, some of the patients declared that they were on the point of collapsing in the attempt. As a rule the usual analgetics had only slight effect, so that in many cases medicaments of the morphia group or dolantin must be administered to the patients. Of these dolantin seemed to have the most favourable effect.

7 of the patients (25 %) had also cerebral symptoms, manifesting themselves as slow cerebration in 3 of them and persisting for some days; moreover 3 of the patients complained of transient loss

Day of disease



Type II.

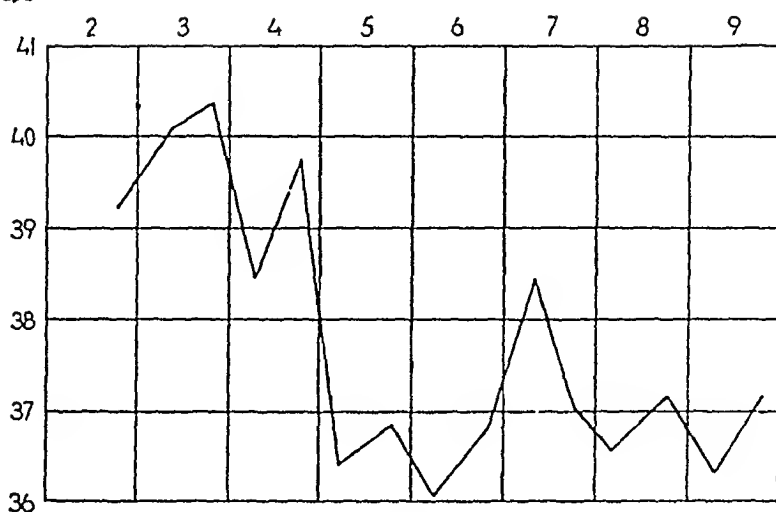
of memory — one of these patients, having been admitted to the hospital under the diagnosis of acute hallucinatory confusion, had been out of bed during his illness at home in spite of a severe head-ache. At last he got completely confused, did not recognize his family, and afterwards he could not remember what had happened some hours previous to the admission. In all these patients the cerebral symptoms, being only of some hours' or at most of some few days's duration, disappeared without leaving any psychic defects.

*Meningeal symptoms:* (Stiffness of neck and back or positive Kernig phenomenon) were present in 7 of our patients (25 %). In 5 of these the cerebrospinal fluid was seen to be pathological with increase of cells and rise of the albumin and globulin values. The increase of cells vanished comparatively soon, the cells consisting at the time of investigation chiefly of lymphocytes. The sugar in the spinal fluid showed normal values. The examination of the spinal fluid was made in still 13 patients. 12 of these patients had normal spinal fluid, in 1 patient, however, there were found 686/3 cells without any sure meningeal symptoms.

*Eye symptoms:*

A slight degree of photophobia was present in some cases, and some of the patients complained of pains in the eyes, but a retro-bulbous tenderness as that in influenza was not found. The pains

Day of disease



Type III.

might undoubtedly be attributed to the severe head-ache localized to the forehead, which most of the patients suffered from. On the other hand a very characteristic feature was the *injection of the episcleral vessels*, which we observed in 16 of our patients, although it has most likely been present in a much greater number of them. In the earliest cases this phenomenon was not given sufficient attention to, and very often the symptom is not present all through the acute period; sometimes it does not occur until the end of this period and may moreover be unilateral.

*Myalgia:* Another important symptom was muscular pains. Occurring from the onset of the disease they lasted in a more or less pronounced degree during the whole of the high-febrile phase. The muscular pains were present in 17 of our patients (58 %), being frequently localized to the muscles of the back (11 cases). In some of these cases the pains were most severe in the region between the scapulae, in others in that across the loins. The pains were very troublesome for the patients and might sometimes be mistaken for genuine stiffness of back. In 3 cases the pains were stated to be most pronounced in the lower limbs, especially around the knee-joints and in the muscles of the calf. In 1 case the muscles of the abdomen and in 2 cases those on the back of the neck were the site of the pains.

The above mentioned symptoms are the most important and those, by means of which the presence of a leptospirosis should be suspected. Besides these there are several other symptoms, which may additionally contribute to the diagnosis.

*Redness in the fauces* was seen in 16 cases, being present on admission in the aggregate cases and consisting in a diffuse redness of the palate and the tonsils. In none of the patients it was attended with any subjective discomfort, at any rate not in a noticeable degree.

*Exanthema*: Exanthema was observed only in 3 cases, appearing from the 5th to the 8th day of disease. In 1 case the exanthema bore a resemblance to roseola and was localized to the arms, in 1 case it was morbilliform and localized to the truncus, and in 1 case it consisted in diminutive dots and bore a close resemblance to the rash of scarlatina. In all the cases it was transient, being only of 1 day's duration.

*Cardio-vascular symptoms*. Cardial symptoms we have observed in 2 patients. One of those was a woman of 49, suffering in advance from a heart-disease, a hypertrofia cordis and hyperthyreoidismus seqv.

Simultaneously with the leptospirosis she got palpitations, and on admission an auricular fibrillation was demonstrated, which persisted during the first 6 days. After this the heart activity became regular, and on the 11th and 16th day of disease the electrocardiogram presented nothing abnormal. The other patient was a woman of 42, who during the last six months had been suffering from a slight degree of dyspnoea; but besides this she presented no symptoms of heart-disease. On the 6th day of disease she got precordial oppression and irregular heart activity, caused by the numerous extra-systoles. Moreover the electro-cardiogram showed flattening of the T-wave in II derivation. The extra-systoles persisted for 6 days, and after that time the electrocardiogram was normal again.

The last mentioned case must be interpreted as a transitory heart-disease, caused by the leptospirosis, whereas in the first case it is impossible to establish whether the leptospirosis or the patient's earlier heart-disease was the main cause of her passing auricular fibrillation. Similar phenomena have earlier been referred to by German authors as regards leptospirosis icterohemorrhagica.

The rest of the patients presented no clinical symptoms of

heart-disease, electro-cardiogram from 5 of these patients showing nothing abnormal.

The *blood-pressure* was measured in 25 patients, in the majority of the cases on admission in the febrile stage. 12 of the patients had a systolic blood-pressure of 110 or less, the lowest being only of 90, and in this patient it kept on being low for about 1 month, rising, however, before the dismissal to 120 systolic.

Our material shows a tendency in the patients towards hypotension, and this observation is in good accordance with earlier statements regarding low blood-pressure in leptospiroses. Similarly it has often been stated that the pulse is comparatively low in diseases due to leptospiroses. In our patients, however, a pulse-frequency of 50 was only found in two cases. In 3 cases the lowest frequency measured was of between 50 and 60, a frequency not differing materially from that seen during the postfebrile phase of most febrile diseases.

*Epistaxis*, which is presumed to be owing to toxic injury to the vessels, was observed in 3 patients.

*Gastro-intestinal symptoms.* Symptoms from the part of the stomach or the intestinal canal were seen in 50 % of the cases, the most frequent manifestations of this kind being vomiting in the acute stage. Two patients had also diarrhoea, and in one of them the diarrhoea was so pronounced during the first days of disease that it was the most striking feature. 1 patient had rather severe abdominal pains at the onset of the disease, so that the disease was mistaken for a case of abdominalia acuta and the patient accordingly admitted to the surgical department, where in the course of some days the cerebral symptoms prevailed, for which reason the patient was removed to the medical department for observation for morbus mentalis.

*Liver:* In 1 patient the border of the liver was palpable below the curvature. In the rest of the patients there was no palpable enlargement of the liver. 1 patient had a just visible jaundice with a plasmacolouring index of 13. In 9 other patients the plasma colouring index was estimated and was found normal. The test was performed between the 5th and the 21st day of disease.

The amount of urobilin in the urine was determined in 9 patients. In 4 of them the reaction was negative, in the remaining 5 urobilin was demonstrated in a urine diluted from 1: 10 to 1: 40.



The above mentioned symptoms are the most important and those, by means of which the presence of a leptospirosis should be suspected. Besides these there are several other symptoms, which may additionally contribute to the diagnosis.

*Redness in the fauces* was seen in 16 cases, being present on admission in the aggregate cases and consisting in a diffuse redness of the palate and the tonsils. In none of the patients it was attended with any subjective discomfort, at any rate not in a noticeable degree.

*Exanthema:* Exanthema was observed only in 3 cases, appearing from the 5th to the 8th day of disease. In 1 case the exanthema bore a resemblance to roseola and was localized to the arms, in 1 case it was morbilliform and localized to the truncus, and in 1 case it consisted in diminutive dots and bore a close resemblance to the rash of scarlatina. In all the cases it was transient, being only of 1 day's duration.

*Cardio-vascular symptoms.* Cardial symptoms we have observed in 2 patients. One of those was a woman of 49, suffering in advance from a heart-disease, a hypertrofia cordis and hyperthyreoidismus seqv.

Simultaneously with the leptospirosis she got palpitations, and on admission an auricular fibrillation was demonstrated, which persisted during the first 6 days. After this the heart activity became regular, and on the 11th and 16th day of disease the electrocardiogram presented nothing abnormal. The other patient was a woman of 42, who during the last six months had been suffering from a slight degree of dyspnoea; but besides this she presented no symptoms of heart-disease. On the 6th day of disease she got precordial oppression and irregular heart activity, caused by the numerous extra-systoles. Moreover the electro-cardiogram showed flattening of the T-wave in II derivation. The extra-systoles persisted for 6 days, and after that time the electrocardiogram was normal again.

The last mentioned case must be interpreted as a transitory heart-disease, caused by the leptospirosis, whereas in the first case it is impossible to establish whether the leptospirosis or the patient's earlier heart-disease was the main cause of her passing auricular fibrillation. Similar phenomena have earlier been referred to by German authors as regards leptospirosis icterohemorrhagica.

The rest of the patients presented no clinical symptoms of

heart-disease, electro-cardiogram from 5 of these patients showing nothing abnormal.

The blood-pressure was measured in 25 patients, in the majority of the cases on admission in the febrile stage. 12 of the patients had a systolic blood-pressure of 110 or less, the lowest being only of 90, and in this patient it kept on being low for about 1 month, rising, however, before the dismissal to 120 systolic.

Our material shows a tendency in the patients towards hypotension, and this observation is in good accordance with earlier statements regarding low blood-pressure in leptospiroses. Similarly it has often been stated that the pulse is comparatively low in diseases due to leptospiroses. In our patients, however, a pulse-frequency of 50 was only found in two cases. In 3 cases the lowest frequency measured was of between 50 and 60, a frequency not differing materially from that seen during the postfebrile phase of most febrile diseases.

*Epistaxis*, which is presumed to be owing to toxic injury to the vessels, was observed in 3 patients.

*Gastro-intestinal symptoms.* Symptoms from the part of the stomach or the intestinal canal were seen in 50 % of the cases, the most frequent manifestations of this kind being vomiting in the acute stage. Two patients had also diarrhoea, and in one of them the diarrhoea was so pronounced during the first days of disease that it was the most striking feature. 1 patient had rather severe abdominal pains at the onset of the disease, so that the disease was mistaken for a case of abdominalia acuta and the patient accordingly admitted to the surgical department, where in the course of some days the cerebral symptoms prevailed, for which reason the patient was removed to the medical department for observation for morbus mentalis.

*Liver:* In 1 patient the border of the liver was palpable below the emvature. In the rest of the patients there was no palpable enlargement of the liver. 1 patient had a just visible jaundice with a plasmacolouring index of 13. In 9 other patients the plasma colouring index was estimated and was found normal. The test was performed between the 5th and the 21st day of disease.

The amount of urobilin in the urine was determined in 9 patients. In 4 of them the reaction was negative, in the remaining 5 urobilin was demonstrated in a urine diluted from 1:10 to 1:40.

The urobilin reaction of the urine was most pronounced between the 8th and the 11th day of disease.

*Palpable enlargement of the spleen* was not found in any of the cases. It is possible that too little attention has been paid to this symptom although once or more in 21 of the cases it has been stated that the spleen was not palpable below the curvature.

*Kidneys.* Albumen in the urine was found in 13 patients. In some of the cases it was probably a febrile albuminuria. Microscopic examinations of the urine showed normal conditions in 7 of these patients. In 6 patients quite a few erythrocytes were found in each section, and granular casts were found only in 3 cases. The pathological formed components of the urine were found between the 5th and 17th day of disease.

Increase in blood urea was demonstrated in 4 patients with erythrocytes in the urine, this increase being, as shown in the following table, most pronounced on the first examination on the 8th to 10th day of disease, and the blood urea very soon dropped to normal.

#### 4. Patients with Azotemia.

Pt. No.	1	2	3	4
day of disease .....	9	10	8	9
blood urea in mg % .....	107	145	49	140
day of disease .....	18	17		18
blood urea in mg % .....	28	51		45

*Peripheral nerves.* Neurological symptoms were seen in 7 of the patients, that is in about 25 %. One of these, however, can not be taken into account, as the patient suffered from an anemia perniciosa with myelopathia.

On the 9th day of disease 1 patient got neuralgiform pains in the upper part of the right arm. (The patient had previous to the admission until the 6th day of disease been treated with sulphani-  
lamide, 1.8 g a day). The neuralgiform pains were attended by a certain amount of reduction in the strength of the muscles, especially that of the biceps without sure neurological degenerative changes. On dismissal after 40 days' hospitalization, during which period the patient had been treated with vitamin BI and myotensor, the pains and the reduction in muscular strength had partially

disappeared. This patient has most likely had a toxic neuritis due to treatment with sulphanilamide.

The remaining 5 cases were very much alike. In 3 of them there was loss of the patellar reflex, but otherwise there were no symptoms of neurological degeneration. Only one of these had an increase of cells in the spinal fluid.

In 2 patients besides loss of the patellar reflex there was flaccid paralysis of the lower limbs.

The 2 cases were very much alike, except for the difference that in one of the patients the spinal fluid was pathological, whereas in the other the latter was normal at the onset of the peripheral nerve-disease. (An examination of the spinal fluid was not made at a later stage.)

A detailed account of the first case has previously been given by Vagn Mortensen together with a review of the literature on neurological changes in leptospirosis and the opinions regarding the causes of these changes.

In the other case the patellar reflex could not be produced from the 4th day of disease and did not recur until after the course of 6 weeks.

For 5 or 6 days the patient was not able to lift his lower limbs from the underlay or to dorsi-flex the ankle; there were moreover sensory disturbances corresponding to the feet and crura, hypæsthesia and hypalgesia increasing to complete analgesia and anesthesia.

The objective changes were symmetrical and not of a permanent nature. The duration of the hospitalization in case of the 2 patients was respectively 62 and 50 days.

*Blood-examinations:* The blood picture was examined on admission, that is from the 3rd to the 10th day of disease. The number of the white blood cells varied greatly, seemingly without any correspondance with the different days of disease; thus 12000 white blood cells were found on the 3rd day of disease and in another patient 2900 on the 4th day of disease.

white blood cells	4000	4—6000	6—8000	8—10000	10—12000	>12000
number of patients	2	9	7	4	5	2

As shown above in the majority of the patients the number of the white blood cells was seen to be lying inside the bor-

der-lines of the normal values, being only in 2 patients higher than 12000.

In most cases the differential count showed a shift to the left of the neutrophil leucocytes; but here too the variations were great, so that on the whole it may be said that the blood examination provided no information of any diagnostic importance worth mentioning.

The *sedimentation test*, being in by far the most cases somewhat increased on admission, was of a certain importance, as it permitted the immediate exclusion of other febrile diseases with normal or only slightly increased sedimentation test.

*The sedimentation test on the admission of the patients.*

number of mm during 1 hour	10	10—25	25—50	50—75	75
number of patients	3	7	11	7	1

As a rule the value of the sedimentation test was rising fast; thus it was found to be 81 mm in a patient on the 3rd day of disease.

In the cases where the value of the sedimentation test could be followed it was seen to remain high for a long time. In 3 patients where the sedimentation test was performed on respectively the 35th and 43rd day of disease the values were found to be respectively 18.20 and 20 mm during 1 hour.

*Diagnosis.*

As recorded in the foregoing the symptomatology of the leptospirosis of the sejroe group presents an intricate picture, so that the clinical diagnosis has to be made through a combination of several of the symptoms. It should be emphasized that the following symptoms: jaundice, enlargement of the spleen and disease of the kidneys in diagnostic respect are of far less significance in these kinds of leptospiroses than in leptospirosis ietero-hemorrhagica, owing to the comparatively rare occurrence of the above named symptoms in leptospiroses of the sejroe group.

Certain characteristic main symptoms, recurring in nearly all the cases, are of particular importance to the diagnosis, namely the *highly febrile temperature, the acute onset of the disease, often accompanied by shivering fits, the headache, which is aggravated in a sitting*

posture and the episcleral injection. Moreover the myalgia, when occurring, are of diagnostic significance.

In all febrile diseases it is very important to let the leptospiroses form part and parcel of the diagnostic considerations similarly to that, which is now the case with febris undulans.

After having seen some cases it is possible to diagnose the disease clinically with comparative certainty. Complete certainty, however, can only be obtained by means of the bacteriological or serological investigation, an investigation which should be made concerning all febrile diseases of obscure origin, just as a serological examination should be made concerning all serous meningeal infections of unknown origin.

### *Differential diagnosis.*

The differential diagnostic difficulties appear from the diagnoses under which the patients were admitted to the hospital; the diagnoses were, in addition to that of leptospirosis: obs. for poliomyelitis, obs. for pneumonia, angina, febris undulans, nephritis, hepatitis, abdominalia acuta, acute confusion, obs. for encephalitis and obs. for meningitis. To these diagnoses may be added that of influenza, a disease which the lighter attacks of leptospirosis are probably often mistaken for.

There can be no doubt that the disease occurs more frequently than it is diagnosed.

### *Prognosis and Treatment.*

The treatment has been symptomatic, and in by far the most cases it has been restricted to confinement to bed and administering of analgetics. In cases with symptoms of peripheral nervous disease accompanied by flaccid paralysis treatment with myotensor and injections of vitamin B was applied.

In 11 of the 29 cases a treatment with sulphathiazole has been tried, partly before the admission and in some few cases also after the admission; however, this medicament does not seem to be able to affect the disease in the slightest degree, as the treated and untreated cases apparently passed off in the same way.

The prognosis is good. On dismissal all the patients were well.

### Summary.

29 cases of leptospirosis of the sejroe group are recorded (leptospirosis sejroe, leptospirosis saxkoebing and an infection with a 3rd., not yet isolated type.

The infection with leptospirae is supposed to originate from leptospirae from mice.

The serological facts are accounted for.

A statement of the intricate symptomatology of the disease is given, and in conclusion diagnostic and differential diagnostic considerations are mentioned.

None of the 29 patients died.

### Literature.

Hermann, K.: Wiener klin. Wochenschrift 1939. pag. 212. — Knudsen, Ivar: Ugeskrift for Læger 100, 14, 1938. — Knudsen, Ivar: Ugeskrift for Læger 102, 1146, 1940. — Kolle, Krans und Uhlenhuth: Handbuch der pathogenen Microorganismen 3. edition, vol. 7. — Mino, P.: Münchener med. Wochenschrift 1941 pag. 96. — Mino, P.: Klinische Wochenschrift 21, 337, 1942. — Mortensen, Vagn: Ugeskrift for Læger, 101, 749, 1939. — Müller, Fr.: Münchener med. Wochenschrift 1894 I, pag. 773. — Petersen, C. Borg og Christensen, Ingemann: Ugeskrift for Læger 101, 697, 1939. — Rimpfen, W.: Ergebnisse der inneren Medicin und Kinderheilkunde 59, 140, 1940. — Rimpfen, W.: Klinische Wochenschrift 21, 341, 1942. — Walch-Sorgdrager: Bulletin of the Health Organisations of the League of nations 1939 vol. 18 pag. 143. — Neue Deutsche Klinik 1934 vol. 12 pag. 369.

---

(Aus der III Medizinischen Klinik in Helsingfors, Professor W. Kerppola.)

## Hypoproteinämie- und Oedembereitschaft während des Krieges.

Von

M. CH. EHRSTRÖM.

(Bei der Redaktion am 2. August 1944 eingegangen).

---

Nach der allgemeinen Auffassung kann Hypoproteinämie durch Serumproteinverlust aus dem Blute und durch mangelhafte Plasmaproteinsynthese entstehen.

Der Proteinverlust aus der Blutbahn geschieht entweder nach aussen wie bei Blutungen, Proteinurie und beim Ablassen von Exsudaten, oder in die Gewebe, wie bei Schock und seröser Entzündung. (Eppinger). In beiden Fällen entsteht eine relative Hypalbuminämie, weil die Albumine die Kapillarwand leichter durchdringen und langsamer als die Globuline regenerieren. Bei Schock und seröser Entzündung kann die Hypoproteinämie durch einen gleichzeitigen Wasserverlust aus dem Blute maskiert werden. Man sieht da normale Serumproteinwerte bei hohen Hämoglobin- und Erythrocytwerten.

Eine unzulängliche Plasmaproteinsynthese kommt bei verschiedenen Formen von Unterernährung, bei gestörter Resorption aus dem Darne und bei Störungen in der Proteinsynthese selbst vor. In beiden ersteren Fällen leidet also der Organismus an »Mangel an Rohmaterial«. Als Beispiel mag die Hypoproteinämie bei Hungeroedem, bei chronischen Diarrhöen, bei Pylorusstenos und bei Sprue (E. Warburg und eigene Beobachtungen) erwähnt werden. Kompliziertere Störungen in der Proteinsynthese liegen den



Hypoproteinämien zu Grunde bei Herzinsuffizienzen, Tumorkachexien, schweren Anämien, Leukämien, Lebercirros, gelber Leberatrophie und bei einigen essentiellen Hypoproteinämien. Auch bei Nephriten und Nephrosen ist die Proteinsynthese wahrscheinlich gestört. (Nonnenbruch, Lichtwitz, Espersen, Holten). In einigen Fällen hat man angenommen, dass die zentrale Regulation der Plasmaproteinsynthese gestört worden sei, (Nonnenbruch, Lichtwitz, M. Ch. Ehrström, Espersen), in anderen Fällen hat man an einen vermehrten Eiweisszerfall und an eine Störung in dem Orte für die Plasmaproteinsynthese selbst (die Plasmazellen?) gedacht.

Auch in diesen Fällen sieht man gewöhnlich eine relative Hypoalbuminämie, die entweder darauf beruht, dass der Organismus eine grobdispersere Eiweisslösung leichter zustandebringt, oder darauf, dass eine solche aus irgend einem Grunde vorzuziehen ist.

Bei den Totalproteinwerten unter 5.5 % oder bei Albuminwerten unter 2.5 % treten gewöhnlich Oedeme auf. Diese hypoproteinämischen Oedeme (nephrotischen Oedeme) folgen nicht dem Gravitationsgesetze in demselben Grade wie die kardialen Oedeme sind aber im Gegensatz zu den elastischen Oedemen bei akuter Glomerulonephritis auffallend weich. Schon ein leichter Druck auf die Haut lässt Vertiefungen zurück, die lange bleiben. Der Eiweissgehalt in der Oedemflüssigkeit ist sehr gering, nach Beckman höchstens 0.1 %, gegen 1 % bei nephritischem Oedem.

Hypoproteinämische Oedeme werden nicht selten mit kardialen oder nephritischen Oedemen kombiniert. Bei Fällen von akuter Glomerulonephritis mit eiweissreicher Oedemflüssigkeit kann nach starker Proteinurie, die einige Zeit gewirkt hat, eine Hypoproteinämie sich entwickeln, wobei die Oedeme einen anderen Charakter nehmen und eiweissarme, nephrotische Oedeme werden. Bei manchen subakuten und halbchronischen Nephriten ist sowohl ein nephritischer Oedemkomponent (= vermehrte Kapillarpermeabilität) als auch ein nephrotischer (= Hypoproteinämie) vorhanden. Wenn das Herz auf Grund der Hypertonie zu versagen beginnt, tritt noch ein kardialer Oedemkomponent hinzu (Fishberg). Bei Herzinsuffizienz kann eine Stasalbuminurie hypoproteinämische Oedeme hervorrufen. (M. Ch. Ehrström). Die Kenntnis dieser Verhältnisse spielt natürlich eine Rolle bei unserem therapeutischen Verfahren.

Während der Kriegsjahre 1942 und 1943 wurde unter Finnlands

Bevölkerung ein Typus von hypoproteinämischen Oedemen beobachtet, dessen Entstehungsmechanismus von Interesse zu sein scheint.

In diesen Jahren war *die akute diffuse Glomerulonephritis* sehr gewöhnlich. Auf der III medizinischen Klinik in Helsingfors wurde die Erfahrung gemacht, dass die Fälle mit Hinsicht auf ihre Oedeme von dem gewöhnlichen Bilde der diffusen Glomerulonephritis abweichend waren. *Die Oedeme waren oft auffallend gross und weich, wie bei Nephrose.*

In 23 Fällen wurden die Serumproteine bestimmt, wobei eine mehr oder minder hochgradige *Hypoproteinämie* konstatiert wurde. Der niedrigste Wert war 3 % Totalprotein. *Dabei ist zu beachten, dass die Proteinurie nie gross war, sondern im Gegenteil oft unbedeutend.*

Dieselbe Erfahrung hat S. Dietrich bei der Feldnephritis in der deutschen Ostarmee in den Jahren 1942 und 1943 gemacht. Dietrich glaubt, dass die Feldnephritis mit der Glomerulonephritis der Friedenszeit nicht identisch sei, sondern dass jene eine spezifische Infektionskrankheit sei, zu deren Symptomen ausser Kapillarschaden auch eine primäre Störung in der Serumproteinbildung gehören sollte. Er lehnt den Gedanken an Unterernährung in seinen Fällen ab und glaubt auch nicht an die Möglichkeit, dass die Hypoproteinämie durch Ausfluss des Serumweißes in die Gewebe entstanden sein könnte. Doch gibt er an, dass der Eiweissgehalt der Oedemflüssigkeit in den ersten Stadien zu 0.7 % aufstieg, und dass die Gewichtszunahme oft 10 kg überschritt. Wenn man berechnet, dass die Bluteiweissmenge etwa 200 g beträgt, bedeutet das, dass ca 70 g oder  $\frac{1}{3}$  des Bluteiweisses dem Oedem gefolgt sei, eine Menge, die die Hypoproteinämie genügend zu erklären scheint. Keine Hydrämie war vorhanden.

Die Hypoproteinämie in meinen Fällen kann nicht erschöpfend erklärt werden als Ausdruck für eine besondere Eigenart bei den Nephriten während des Krieges. Es erwies sich nämlich, dass *die Oedeme auch bei Herzinsuffizienz oft einen nephrotischen Charakter hatten, und die Serumproteinanalysen offenbarten nicht selten eine hochgradige Hypoproteinämie* (der niedrigste Wert 2.7 % Total-eiweiss). In einigen Fällen lag eine leichte Stasproteinurie (ad 1.5 pro mille) vor, meistens aber war der Urin proteinfrei.

Den wirklichen Wert bei diesen Hypoproteinämien während

des Krieges bekommt man durch Vergleichung mit Serumproteinanalysen bei Nephriten und Herzinsuffizienzen während des Friedens. Als Vergleichungsobjekt sind solche Fälle aus den Jahren 1937 und 1939, erwähnt worden, die mit Hinsicht auf die Dauer und die Grösse der Proteinurie in einem möglichst hohen Grade den Fällen aus den Kriegsjahren entsprechen haben. Die Serie von Fällen aus der Friedenszeit enthält jedoch etwas mehr Fälle mit hochgradigerer Proteinurie. |d

Die Durchschnitzahlen für die Serumproteinwerte in den beiden Serien sind folgende:

		Total-proteine	Albumine	Globuline
1942—43	Nephriten .....	5.4 %	2.9 %	2.5 %
	Herzinsuffizienzen .....	5.5 %	3.0 %	2.5 %
1937—39	Nephriten .....	6.9 %	4.0 %	2.9 %
	Herzinsuffizienzen .....	7.1 %	4.0 %	3.1 %

Die Nephriten und die Herzinsuffizienzen während des Krieges haben also niedrigere Serumproteinwerte als die Fälle während des Friedens. Der Unterschied bei den Nephriten ist 1.5 und bei den Herzinsuffizienzen 1.6 % Totalproteine. Die Differenzen beruhen zum grössten Teile auf den Albuminen. Die Unterschiede zwischen den Globulinwerten der Serien machen nur 0.4 % für die Nephriten und 0.6 % für die Herzinsuffizienzen.

Nur in einem Falle von Nephritis aus den Kriegsjahren wurde der Eiweissgehalt in der Oedemflüssigkeit bestimmt. Der war hoch, wohl 1.0 %. Die Hemoglobin- und Erythroeytwerte im Blute waren in den akuten Nephritisfällen nicht herabgesetzt.

Da Proteinurie nicht allein an der vermehrten Hypoproteinämie tendenz der Kriegsjahre Schuld sein kann, kann dieselbe nur entweder durch eine gesteigerte Kapillarpermeabilität mit vermehrtem Ausfluss des Eiweisses in die Gewebe oder durch eine defekte Proteinsynthese erklärt werden. Die beiden Möglichkeiten scheinen in Betracht kommen zu können.

Seit dem Jahre 1940 hat die Bevölkerung von Helsingfors (wo die Patienten herkommen) auf fett- und eiweissarmer Kost gelebt. Besonders ist das animalische Eiweiss knapp gewesen, hat

zeitweise sogar ganz gefehlt. Trotzdem sind keine Fälle von wirklichen hypoproteinämischen Hungeroedemen vorgekommen, und eine von O. Turpeinen ausgeführte Untersuchung über die Serumproteinwerte bei den Klienten auf der Poliklinik des Krankenhauses Stengård zeigte, dass die Serumproteinwerte der Einwohner von Helsingfors durchaus normal waren. Deshalb kann man kaum voraussetzen, dass die Blutproteine der Nephritis- und Herzinsuffizienzpatienten primär herabgesetzt gewesen seien.

Insbesondere in dem Jahre 1942, wo die Versorgungsverhältnisse besonders schwer waren, wurden jedoch zahlreiche Fälle von Oedem beobachtet, die mit Hypoproteinämie nicht kombiniert waren. Diese kamen speziell bei Frauen vor und waren auf das Unterhautgewebe im Gesicht und in den Beinen beschränkt. Durch ihr Aussehen und durch ihre wechselnde Intensität erinnerten diese Oedeme an angioneurotische Oedeme. Sie reagierten günstig auf Kalk- und Hefekur in Kombination mit extra Zugabe von Butter und Fleisch. Vieles sprach dafür, dass *die Oedeme auf einer gestörten Kapillarpermeabilität beruhten, die im Zusammenhang mit der Krisenzeit und der defekten Ernährung war.*

Es scheint also berechtigt, bei den Patienten während des Krieges eine gestörte Kapillarfunktion vorauszusetzen. Es ist wohl auch möglich, dass eine weitere Beschädigung der Kapillargefässe durch die Entstehung einer Nephritis oder einer Herzinsuffizienz eine so stark vermehrte Kapillarpermeabilität zu Folge hätte, dass Ausfluss in die Gewebe eine Hypoproteinämie hervorrufen könnte.

Doch muss man auch die Möglichkeit einer unzulänglichen Proteinsynthese beachten, die auf dem Mangel an Eiweiss in der Nahrung beruhen könnte. Der Organismus versucht mit allen Mitteln ein normales Bluteiweissniveau beizubehalten. Dabei verfügt derselbe unter normalen Verhältnissen über eine gewisse Menge von Depot-Eiweiss. Plasmainjektionen haben nämlich erwiesen, dass sehr grosse Eiweissdosen in Depot verschwinden können, auch bei so gut wie normalen Eiweisskonzentrationen im Blute, was nicht der Fall zu sein scheint, wenn der Organismus vollgeladen ist (Hedenius). Es scheint deshalb sehr glaubenswert, dass weil die Blutproteinsynthese bei eiweissarmer Kost äusserst angestrengt ist, ein Proteinverlust aus der Blutbahn, entweder durch Ausfluss in die Gewebe oder durch Proteinurie katastrophale Folgen haben kann.

Die Hypoproteinämie bei den Nephriten und Herzinsuffizienzen während des Krieges in Finnland scheint also durch ein Zusammenwirken von disponierenden Faktoren — (gestörte Kapillarfunktion, die durch die Krisenzeit und die defekte Ernährung bedingt ist und mangelhafte Plasmaproteinsynthese) — und von auslösenden Faktoren (Eiweissausfluss durch die Kapillarwand und Proteinurie) zustandezukommen. Mit anderen Worten, es ist eine Hypoproteinämiebereitschaft vorhanden. Hypoproteinämie und Oedem werden manifest, wenn solche Faktoren wie Proteinurie oder Kapillarpermeabilitätssteigerung hinzutreten.

#### Literaturverzeichnis.

Beckman: ref. Fishberg. — Dietrich: Klin. Wschr., 22, 715 (1943). — Ehrström, M. Ch.: Finska Läkare Handl., 79, 59 (1936). — Eppinger: Die seröse Entzündung. Wien 1935. — Espersen: Ugeskr. f. Læg., 100, 847 (1938). — Fishberg: Hypertension and Nephritis, Philadelphia 1940. — Hedenius: Nord. med., 21, 125 (1944). — Holten: Nord. med., 12, 3059 (1941). — Lichtwitz: Pathologie der Funktionen und Regulationen, Leiden 1936. — Nonnenbruch: »Knolls mitt. f. Ärzte. Jubiläumsausgabe 1936. — Turpeinen, O.: Wird später veröffentlicht. — Warburg, E.: Nord. med., 2051 (1938).

---

## REVUE DES LIVRES:

V. Tronconi, I neurinomi dell'acustico. Contributo clinico ed anatomo-patologico. Milano 1943, 152 p. avec 24 figures et 17 planches.

Les tumeurs de l'acoustique qui, dans le classement qu'en a fait Cushing occupent la troisième place parmi les tumeurs cérébrales primaires (gliomes 56.2 %, méningomes 17.7 %, tumeurs de l'acoustique 11.5 %) ont, depuis que Sandifort les a décrites et représentées en 1777, attiré le vif intérêt des cliniciens et des pathologistes. De nos jours, le diagnostic est très sûr et les résultats du traitement chirurgical sont, grâce surtout à Cushing et à Olivecrona, très satisfaisants. Par contre, il y a de grandes divergences d'opinions concernant leur histopathologie et leur histogénèse.

La présente monographie, qui donne un bon aperçu des recherches effectuées dans ce domaine, est fondée sur un nombre relativement petit de cas observés par l'auteur lui-même, soit 9 cas de tumeur unilatérale et 2 cas de tumeur bilatérale (dont un cas avec neurofibromatose généralisée). L'auteur est un médecin neurologue et il s'intéresse principalement à la sémiologie, au diagnostic et à l'anatomie pathologique de ces tumeurs. Ses développements thérapeutiques se limitent à une courte analyse du traitement chirurgical.

Tronconi interprète à sa manière l'histologie des tumeurs de l'acoustique. Il ne croit pas devoir se rallier aux auteurs qui les ont considérées comme purement névrogliales, comme des neurilemmomes, mais il est d'avis que les fibrilles de la tumeur sont de nature pré-collagène. Comme on ne peut pas, de l'avis de l'auteur, séparer les cellules de la gaine de Schwann de celle de l'endoneurium, on doit considérer que ces tumeurs se produisent par suite d'une pro-

lifération des éléments totipotents des gaines du nerf, éléments qui donnent d'abord naissance à une nouvelle formation mixte de tissus neurilemmiques et histiocytaires, au sein de laquelle les éléments conjonctifs domineront en raison de leur puissance supérieure de prolifération. L'opinion de Tronconi sur ce point coïncide avec celle de l'auteur de ce compte-rendu, à savoir que ces tumeurs doivent être considérées comme des tumeurs mixtes neuro-conjonctives. Un certain nombre de travaux importants on été omis dans l'abondante bibliographie et notamment: Antoni, Rückenmarkstumoren und Neurofibrome, München 1920, ouvrage souvent cité dans le texte, et Cushing, Intracranial Tumours, Springfield-Baltimore 1932.

*F. Henschen.*

---

## Ouvrages envoyés aux Acta medica scandinavica.

*De nordiska kriminalistföreningarnas årsbok 1942—43.* 296 s.  
A.-B. Allhems förlag, Malmö 1944.

W. Zillmer: *Kriegschirurgie im Reserve-Lazarett.* 3. Auflage. 600 S. Preis: geb. RM 18:—, Verlag von Theodor Steinkopff, Dresden und Leipzig, 1944.

Hans-Georg Scholtz: *Die Ischias.* 2. umgearbeitete und ergänzte Auflage. 125 S. 24 Abb. Preis: geh. RM 6.50. Verlag von Theodor Steinkopff, Dresden und Leipzig 1944.

*Report of the inter-departmental committee on medical schools.* Ministry of health. Department of health for Scotland. 313 p. Price: 4 s. 6 d.net. His Majesty's stationery office. London, 1944.

E. G. Steinke: *Kleines physikalisches Praktikum.* 2. und 3. Auflage. 276 S. 132 Abb. und zahlreiche Messtabellen und graphische Darstellungen. Preis: geb. RM 11.—, Verlag von Theodor Steinkopff, Dresden und Leipzig 1944.

---





From the Fourth Medical Service of St. Erik's Hospital, Stockholm.

## Normal Esterases and Pancreatic Lipase in the Blood.

A Study with new Chemical and Clinical Methods  
(A Second Secretin Test).

By

HENRIK LAGERLÖF.

(Submitted for publication November 16, 1944).

---

### Historical Review.

Determination of the amylase content in blood and urine is now considered an important means for the diagnosis of acute pancreatic diseases. Although it has long been known that the content of esterase in the blood also increases in these diseases, determinations of the blood esterase are not given the same significance. This is because the methods used are not satisfactory, either from a theoretical or technical point of view.

The present communication points out the earlier methodologic deficiencies and presents a new and simple method for determining the pancreatic lipase in the blood.

*Definition of Esterase and Lipase.* — By esterases are meant enzymes which catalyze the reaction  $\text{RCOOR} + \text{H}_2\text{O} \rightleftharpoons \text{RCOOH} + \text{ROH}$ . These enzymes have both a splitting and a synthesizing effect. Only their splitting effect will be discussed in the following, since it is sufficient for the classification and determination of the esterases.

Esterases which split organic esters of low molecular weight are called esterases in the narrower sense, the ones which split glyce-

rin esters of fatty acids of high molecular weight, i.e., fat, are called lipases. The substrate specificity is only relative. Esterases in the strict sense have a weak effect on fat as well, and the lipases on esters of low molecular weight.

*Methods of Determination.* — The esterases are determined with the aid of the changes in the substrate which occur on the hydrolysis of esters. Since the activity of the esterases is greatly influenced by concomitant substances, attention must be given to these substances in the determination. In the case of pancreatic lipase, compensating inhibition and activation are generally produced with albumin and calcium oleate (40, 41). The most common methods of determination are based on one of the following principles.

a. Titrimetric determination of the acid formed. The substrates most commonly used are olive oil, tributyrin and methyl butyrate.

b. Stalagmometric determination of the unsplit ester. The esters tributyrin or monobutyrin, which greatly reduce the surface tension, are used for the substrate. As the concentration of substrate decreases during the hydrolysis, the surface tension increases, and the number of drops per volume decreases. The splitting of the substrate and the amount of esterase are then determined from the difference between the original number of drops and those after a certain period of hydrolysis.

c. Gas analysis. The amount of carbon dioxide equivalent to the acid liberated from the ester is measured. Tributyrin is one of the substrates used.

*Composition of the Esterases.* — Kraut and Pantschenko-Jurewicz (21) gave convincing proof that the esterases, like many other enzymes, consist of combinations of an active group, called agon, which causes the specific catalytic action, and a colloidal carrier, pheron, which causes fine differences in the specificity. These substances are inactive in themselves, but when they combine they form the active enzyme called symplex. The equilibrium between agon and pheron is determined by the dissociation constant of symplex: 
$$\frac{\text{agon} \times \text{peron}}{\text{symplex}} = \text{equilibrium constant.}$$
 The constant is not particularly small and is dependent upon the pH.

The agon is often unstable and may undergo irreversible conversion to anagon, as it is called, which cannot combine with the phe-

ron to form symplex. In this case, more symplex is dissociated and the activity decreases successively. If the amount of pheron in the solution is increased, less agon is split off and the inactivation decreases. On the other hand, an increase in the pheron has little influence upon the amount of symplex, i.e., upon the activity.

*Pancreatic Lipase and Liver Esterase.* — The pancreatic esterase is a real lipase, the liver esterase an esterase in the strict sense of the word. Willstätter and Memmen (42) gave the following comparative figures for their effect on different substrates:

One gram of pancreatic powder corresponds  
to 10,600 Gm of liver powder in the splitting of olive oil,  
» 100 » » » » » » » tributyrin,  
» 0.4 » » » » » » » methyl butyrate.

The pancreatic lipase and liver esterase differ in other respects as well. When the pancreatic lipase is pre-treated with a sufficient amount of quinine, it loses its power to split tributyrin. On the other hand, it is highly resistant to pre-treatment with atoxyl (30). The conditions are reversed in the case of the liver esterase (29).

The activity of pancreatic lipase can be centupled by the addition of calcium oleate and albumin to the substrate (41). Liver esterase is inhibited by these substances.

Esterase solutions from pancreas and liver contain different kinds of pheron. If a pancreatic preparation with a high agon content is mixed with a liver preparation containing little pheron, the equilibrium is displaced and some of the pancreatic lipase is converted to liver esterase. Virtanen and Suomalainen (37) observed displacements of this kind *in vivo* after injecting pancreatic lipase into rabbits. When they examined the organs afterwards, they found that the content of esterase in the liver had increased. This esterase was typical in every respect of liver esterase.

#### *Normal Serum Esterase.*

*Variations.* — The esterase content varies considerably in different healthy persons. It also varies considerably from time to time in the same subject, without any obvious external cause. The esterase content is not appreciably influenced by the ingestion of food, muscular exercise, nervous excitement, or by menstruation or pregnancy. Nor is it related to age, sex or weight (38).

*Reaction to Atoxyl and Quinine.* — Rona and his co-workers (26, 29, 30, 31) and Jedlička and Kreisinger (19) studied the resistance of different animal sera to atoxyl and quinine. The serum esterase of dogs was easily inhibited by quinine but highly resistant to atoxyl. Rabbit and human serum were inhibited both by atoxyl and by quinine. The inhibition was dependent on the period of time and the amount of poison. Quinine was maximal inhibiting immediately, whether it was added directly to the tributyrin or to the serum. Atoxyl had to be added directly to the serum to obtain its maximal effect, which then occurred in thirty minutes. The amount of poison affected the inhibition according to the formula  $\frac{C_A - C_B}{\log B - \log A} = C$ , in which  $C_A$  and  $C_B$  represent the reaction constants and B and A the concentrations of poison. The completely inhibiting concentration of poison could be reckoned from this formula if the reaction constants with two different poison concentrations were known. At a pH of about 7.6 it was 0.15 mg for atoxyl, when the total volume of the mixture was 35 ML., and the corresponding figure for quinine was 1.6 mg. Reckoned in per cent, the inhibition was equally great for different amounts of enzyme. The inhibition with quinine increased with a rising pH.

When the sera from different animals were mixed, the lipases retained their properties in relation to the poisons. This was also the case when the sera were mixed with purified enzyme from liver and pancreas.

After these observations, Rona, Petow and Schreiber (32) suggested that a study be made of the serum esterases resistant to atoxyl and quinine in pancreatic and liver diseases.

*Reaction to Calcium Oleate.* — The effect of calcium oleate on normal serum esterase has never been tested, although it has long been known that the oleate accelerates the hydrolysis of tributyrin with pancreatic lipase several thousand per cent.

Methods in which calcium oleate is added to the tributyrin have been used by several authors (12, 13, 14, 15, 19) to demonstrate the passage of lipase into the blood in experimental and clinical pancreatic disease.

Grassberger (13, 14) observed an increase of esterase in pancreatitis to at the most three times the highest normal values. The

reason why he observed such a small increase was probably the low pH prevailing during his experiments — 7.6. At this pH calcium oleate has a much smaller activating effect on pancreatic lipase than at the pH used by me.

The other authors (12, 15) observed only a slight increase of the serum esterase, if any, in pancreatic disease. This is probably because, judging from their material, none of the sera tested contained any great amount of pancreatic lipase.

*Function.* — Plattner (24) showed in 1926 that blood inactivates acetylcholine. In 1930 Engelhart and Loewi (9) established that this inactivation was due to a hydrolyzing enzyme. Wahlqvist studied the relation between the methyl butyrate, tributyrin and acetylcholine splitting power of human plasma in cataphoretic experiments and inhibition experiments with quinine, atoxyl and physostigmine. The tributyrin and the acetylcholine esterase activity showed a pronounced co-variation. He concluded that the hydrolysis of acetylcholine by human blood plasma is brought about by the same enzyme which produces the hydrolysis of tributyrin. Wahlqvist (38) also determined the plasma esterase activity in different physiologic and pathologic conditions. His investigations did not support the view that the plasma esterase is engaged in the finer regulation of the vegetative functions of the body. Wahlqvist pointed out, however, that the acetylcholine hydrolyzing ability of plasma probably prevents an accumulation of acetylcholine in the blood, and he suggested that this action represented the main physiologic function of the plasma esterase.

*Origin.* — The source of normal serum esterase is obscure. As earlier mentioned, it reacts differently to poisons than pancreatic lipase and liver esterase. It is also unlike the esterase which occurs in the red blood corpuscles (34). It is probable that only a small part, if any, of the esterase active at the pH of the blood comes from the pancreas. Thus Ficsinger, Albeaux-Fernel and Gajdos (10) could not observe any change in the activity of the serum esterase after pancreatectomy in dogs. Jedlička and Kreislinger (19), on the other hand, observed a 25 to 50 per cent drop in the serum esterase after similar operations, but they determined the lipase at a pH of 8.6 after the addition of calcium oleate and under such conditions the contribution of the pancreatic lipase to the hydrolysis is increased by several thousand per cent.

*Serum Esterase in Pancreatic Disease.* — Animal experiments show that esterase diffuses into the blood in cases of pancreatic disease or stasis in the pancreatic ducts (6, 17, 19). Since such serum contains esterases of different origin, it has been attempted separately to determine the fraction originating from the pancreas. The methods are founded either on the resistance of pancreatic lipase to atoxyl, or on the great olive oil splitting power of pancreatic lipase.

As regards the occurrence of atoxyl-resistant tributyrin splitting esterase in the serum in pancreatic disease, the reports are as varying as they are numerous. While, for example, Schmitt (33) and Beckman (2) consider that the atoxyl-resistant esterase is elevated in the majority of cases of both acute and chronic disease in the pancreas, Popper and Scholl (25) say that elevations are much less regular than in the case of serum amylase.

It should be pointed out in this connection that a rise in the atoxyl-resistant esterase has been observed in diseases where there is no suspicion of pancreatic injury, for example, in pernicious anemia (35), cancer in various organs (2, 3, 11, 23), thyrotoxicosis (2, 11) and chronic arthropathy (2).

The variations in the results obtained for atoxyl-resistant esterase in the blood are largely due to lack of standardization of the method and technical errors in its performance. Different pH's during the digestion have been used, and different proportions of the reagents. Generally no consideration has been given to the temperature during the reaction and during the counting of the drops, the tests being done at »room temperature». Moreover the esterase activity has been expressed as the difference between the tributyrin drop number before and after the hydrolysis. The figures obtained in this manner can only be compared when stalagmometers of the same construction and the same number of drops for water are used. Because of the variations and faults in the technic and in the expressions for the esterase activity, it is impossible to give any normal values for the atoxyl-resistant esterase and consequently to know what values should be regarded as definitely elevated.

It is evident from studies of single cases that the esterase may occasionally be elevated some hundred per cent of the normal values in cases of acute pancreatic disease. The striking discrepancy

between this small elevation and the great increase of amylase in blood and urine is due to the small tributyrin splitting power of unactivated pancreatic lipase as compared with normal serum esterase (p. 25).

Cherry and Crandall (6) introduced a method for the determination of the lipase content of serum with olive oil as the substrate. The fatty acid formed on the hydrolysis of one milliliter of olive oil is titrated with twentieth normal sodium hydroxide, using phenolphthalein as indicator, after the addition of 3 Ml. of 95 per cent alcohol to 6.5 Ml. of the digestion mixture.

This method is liable to objections. The time of hydrolysis is very long, twenty-four hours. The amount of alcohol used for the titration is not sufficient to dissolve the olive oil and the fatty acid formed. Thus the titration is done in a heterogeneous medium. Every drop of sodium hydroxide causes the mixture to assume a rosy tint, which disappears after a few minutes. This being the case, the end point of the titration is much a matter of personal opinion.

There is also no possibility to determine the amount of lipase from the titration value as nobody has shown any relation between these values and the amount of lipase.

Comfort and Osterberg (7) and Johnsson and Bochs (18) and others who used the method reported normal lipase values up to 1 to 1.5 Ml. of sodium hydroxide solution and values up to 5 to 6 Ml. in cases of acute pancreatic disease. I found no significant amount of pancreatic lipase in normal blood serum. Since serum esterase does not demonstrably split olive oil, the high normal lipase values reported by the American authors are probably referable to errors in titration.

*Esterases in the Red and White Blood Corpuscles.* — The red blood corpuscles contain large quantities of atoxyl-resistant tributyrin splitting esterase, which is liberated by hemolysis (5, 34). They also contain quinine-resistant esterase. It is not known whether the esterase is formed in the blood corpuscles or are absorbed from the serum. Their variations under pathologic conditions have not been investigated. The white blood corpuscles also contain esterase (1, 43).



## New investigations.

### *Method.*

*Stalagmometric Technic.* — Stalagmometers according to Traube were used. The greater part of the stalagmometer is enclosed in a glass jacket, in which the water of the water bath circulates. The water is driven by a centrifugal pump, which also serves as a mixer for the water bath. Before every series of experiments the stalagmometer is carefully cleaned with tenth normal potassium hydroxide, water, alcohol, ether, alcohol and water, in the order given. It has been found inadvisable to do this cleaning after each single determination.

The stalagmometer is mounted firmly on a stand, protected from draught and vibration, and care is taken not to move it until all the readings which refer to one series of lipase determinations are done. A rubber tube is attached to its upper end for sucking up the fluid in the stalagmometer, the tube being closed with a clip. Before the readings the motor of the water bath is stopped. The counting of the drops is facilitated by a relay arrangement. The drops fall between two sloping lead plates, so that every time a drop falls, an electrical circuit is closed, which causes an electromagnet to attract an iron plate fastened to a spring. The reading may be graphically arranged or done by counting the taps. Thus the counter has his eyes free for reading the meniscus. The position of the meniscus can be estimated within one or two degrees on the scale. Thus it is possible to calculate the number of drops to practically a tenth of a drop.

### *Solutions Required.* —

1) Saturated tributyrin solution: 10 drops of purified tributyrin (41) are added to 1 liter of water and shaken for one or two hours. The solution is filtered and put in a refrigerator for at least twelve hours. Kept there, it is usable for the next forty-eight hours.

2) Buffer solutions:

a) 1 part of a 4 molar solution of  $\text{NH}_4\text{OH}$  + 4 parts of a 4 molar solution of  $\text{NH}_4\text{Cl}$  (pH about 8.8).

b) 1 part of a  $\frac{1}{3}$  molar solution of  $\text{KH}_2\text{PO}_4$  + 4 parts of a  $\frac{1}{3}$  molar solution of  $\text{Na}_2\text{HPO}_4$ .

3) 0.25 per cent calcium chloride solution.

4) 0.5 per cent sodium oleate solution.

5) 0.2 and 2 per cent atoxyl solution.

6) 0.5 per cent quinine sulphate solution.

*Procedure.* — The tributyrin is warmed to room temperature. For every esterase determination 50 ml. are pipetted over to 100 ml. Erlenmeyer flasks, which are then placed in the water bath. Ten to sixty minutes later 1 ml. of buffer and in some experiments 1 ml. of sodium oleate and 1 ml. of calcium chloride and 1 ml. of quinine sulphate in the order given, are added. At a time noted to the second 1 ml. of serum or heparinized blood or 1 ml. of atoxyl-poisoned serum or heparinized blood (1 ml. of serum or blood + 1 ml. of atoxyl mixed and allowed to stand thirty minutes at room temperature) are added. The drop counting is then begun as soon as possible, generally ninety seconds later. The number of drops at the beginning of the hydrolysis is extrapolated from the value thus obtained.

Further drop countings are done during the course of the hydrolysis. Drop differences of 5 to 15 drops are desired. The drop counting after  $t$  minutes of digestion is begun at  $t - \frac{r}{2}$  seconds, the running out time being  $r$  seconds.

The decrease in the tributyrin concentration is determined from the difference in the number of drops of the substrate before and after the hydrolysis. The determination is done with the aid of an empirical curve, giving the reduction in the number of drops as the tributyrin concentration is decreased, while the composition of the substrate is kept constant otherwise (22) (fig. 1).

*Expression for Esterase Concentration.* — Rona and Ehsen (27) found that the splitting of tributyrin with blood esterase follows approximately a mono-molecular course, and that the amount of enzyme is proportional to the reaction constant. This is also true of the lipase of duodenal juice whether it is determined with (22) or without (8) the addition of calcium oleate, and also of the pancreatic lipase which diffuses into the blood (p. 23). In this study, therefore, the reaction constant times 1000 is used to express

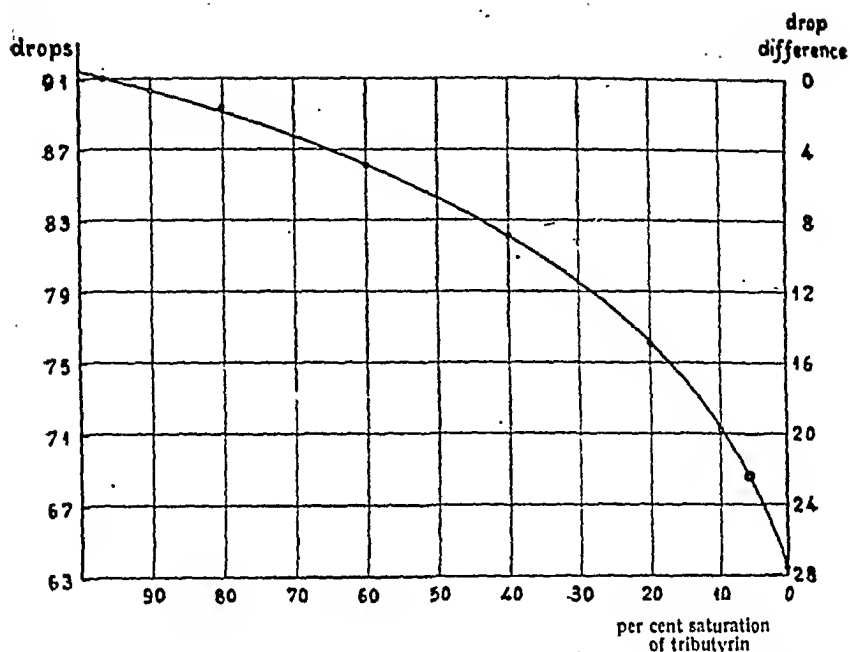


Fig. 1. Relation between number of drops and per cent saturation of tributyrin.

the esterase activity. The reaction constant is calculated from the formula  $C = \frac{1}{t} \cdot \log \frac{91}{x}$ , where  $t$  represents the digestion time in minutes and  $x$  the concentration of the tributyrin at the time  $t$ , measured in per cent of saturation.

The work required a new curve giving the relationship between the decrease in drops and the activity of esterase. It was constructed on the basis of the empirical curve in figure 2 and the formula for the mono-molecular reaction. The fall in the number of drops after thirty minutes of hydrolysis was plotted against the esterase activity per milliliter serum of blood (fig. 2).

#### Sources of Error. —

*Different stalagmometers.* — When Traubes stalagmometers (36) are used the number of drops in a solution is reversely proportional to its surface tension in relation to water and consequently to the stalagmometer's drop number for water, if the drops attain maximal size before they fall. This they always do if

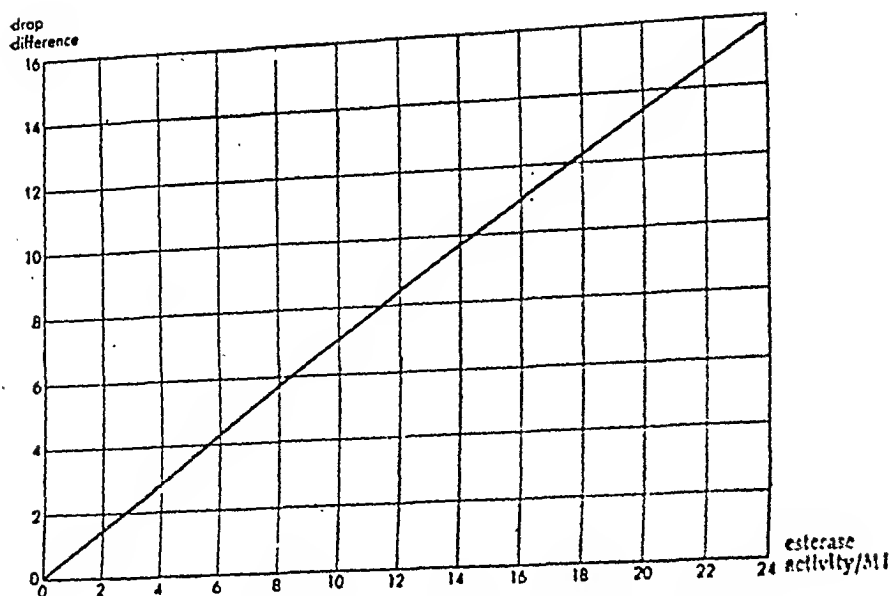


Fig. 2. Standard curve of esterase. 30 minutes digestion, 1 Ml. serum.

less than twenty fall per minute and generally do if less than forty fall per minute. The same drop numbers are obtained with different stalagmometers when the number of drops in a solution are converted to the corresponding number of drops for a normal stalagmometer, which has a drop number of 100 for water at 20 C. (1). The conversion is done according to the formula:

$$\frac{\text{The drop number} \times 100}{\text{The drop number of the stalagmometer for water}} = \text{the drop number for the normal stalagmometer.}$$

The Rona-Michaelis «Schnelltropf» pipette (28) gives greater drop figures for tributyrin solutions than corresponds to the solutions' surface tension in relation to water. When esterase is determined accordingly, larger drop differences are obtained with stalagmometers of this type than with ones of the Traubes type (table 1).

*Effect of temperature on the number of drops.* The temperature has only a slight effect on the surface tension. Accordingly it has little influence on the number of drops when Traubes stalagmometers are used. This is seen from table 1, where the number of drops at 16 and 20 C. for water and mixtures of serum, phosphate buffer and atoxyl with tributyrin solutions of different concentra-

tions are compared. The mixtures were such as occur in the determination of atoxyl-resistant esterase according to the original method of Rona, Petow and Schreiber (32).

When the Rona-Michaelis »Schnelltröpf» pipette is used, the temperature has a large influence on the number of drops (4) (table 1). The number of drops for pure water is less influenced than those for mixtures containing sera, where differences as high as 8.6 drops were observed.

*Temperature during the hydrolysis.* — The temperature during the hydrolysis is of great importance to the esterase effect. The drop difference after ninety minutes of digestion at 16 and 26 C. with the original method of Rona, Petow and Schreiber for atoxyl-resistant esterase differs by about 300 per cent (table 1). The im-

Table 1.

*Comparison Between the Drop Numbers of a Traubes Stalagmometer and a Rona-Michaelis Drop Pipette.*

The figures are calculated for stalagmometers with a drop number for water of 100 ML.

Traubes stalagmometer: Volume 8.0 ML., running out time 140 seconds.  
Drop number for water 61.0 ML.

Rona-Michaelis drop pipette: Volume 3.05 ML., running out time 45 seconds.  
Drop number for water 71.3 ML.

Tributyrin, % saturation	Addition of 3 ML. serum + 3 ML. buffer pfr 7.65 + 1 ML. 0.2 % atoxyl.	Temp. C.	Traubes					Rona-Michaelis				
			Time of hydrolysis min.			Difference		Time of hydrolysis min.			Difference	
			0	3	90	26 C.- 16 C.	3-90 min.	0	3	90	26 C.- 16 C.	3-90 min.
0	0	16	99.5					98.0				
0	0	20	100.0			1.2		100.0			2.8	
0	0	26	100.7					100.8				
0	+	16	101.0			1.4		106.2			8.6	
0	+	26	102.4					114.8				
25	+	16		118.1		0.9		120.2			8.0	
25	+	26		119.0				128.2				
50	+	16		126.3		1.1		131.7			6.7	
50	+	26		127.4				138.4				
100	+	16	136.8	131.2		5.6		149.9	139.8		8.1	10.1
100	+	26	137.0	120.4		0.2	16.6	158.0	131.6			26.4

portance of this fact is obvious when the estimations are done at »room temperature».

*Tributyrin solution.* — Commercial tributyrin contains impurities which increase the drop number of the solution and decrease the drop difference, especially towards the end of the hydrolysis. These impurities can be removed by washing the tributyrin with water eleven times (41).

No difference in the drop number or rate of hydrolysis was observed when the tributyrin solution was saturated at 0 C. and at room temperature.

*Atoxyl solution.* — The atoxyl solution is not permanently stable. The literature states that it should be prepared from oxygen-free water and kept protected from light (2). These precautions were observed in the present study. The solution was freshly prepared every fourteen days and kept in a refrigerator. No difference was observed between freshly prepared and fourteen-day-old solutions in the esterase determinations.

In the first experiments a similar amount of atoxyl was used as in the Rona, Petow and Schreiber original method, and the same is true of the time of poisoning. In the final method, a ten times greater amount of atoxyl was employed without alteration of the time.

### *The Blood Esterase in Experimentally Produced Stasis in Human Pancreatic Ducts.*

*Anatomic Structure of Oddi's Sphincter.* — According to Hendrickson's classical description of 1898 (16), Oddi's sphincter consists of the three following parts:

1) A circular band around the choledochus, the sphincter choledochus.

2) A longitudinal band in the angle between the choledochus and the duct of Wirsung. Contraction of this band facilitates the flow of bile and pancreatic juice, according to Boyden and his co-workers.

3) A both circular and longitudinal band around the ampulla of Vater. Contraction of this band, which varies greatly in development, is thought to shut off the flow of both bile and pancreatic juice to the intestine. If the duct of Wirsung has its orifice a certain

distance away from the orifice of the ampulla, as is often the case, contraction of this bundle may admit the pressing of bile into the pancreas or of pancreatic juice into the biliary ducts, depending on where the pressure is greater.

*Effect of Morphine on Oddi's Sphincter.* — Experiments on animals (20) and on humans (39) have shown that morphine raises the pressure in the biliary ducts, apparently because of contraction of Oddi's sphincter or parts thereof (sphincter choledochus). Still unpublished experiments on the effect of morphine on the secretion of duodenal juice indicate that this contraction also involves the muscular bundles which encircle Vater's papilla. Thus morphine inhibits the delivery of the pancreatic juice after intravenous administration of secretin, and in this way often causes a rise in the blood amylase. In many cases the subject then experiences pain characteristic of biliary dyskinesia, the situation of which varies. It is often felt deep down in the left of the epigastrium and radiates along the left costal margin and out in the back, and is combined with hyperesthesia in the corresponding regions. At the same time the whole pancreatic region may become tender and remain so for several days. There thus develop clinical signs of mild pancreatic disease. This reaction was observed chiefly among cholecystectomized patients but also occurred in persons with a normally functioning gallbladder.

*Plan of Experiments.* — In order to learn whether the diffusion of amylase from the pancreas to the blood which sometimes occurs after the simultaneous injection of morphine and secretin was accompanied by a similar discharge of pancreatic lipase, a study was made of a number of experimental subjects who showed a large increase in blood amylase. Morphine and secretin were injected in the morning with the subject in the fasting state and specimens of blood were removed at varying intervals afterwards. The patients remained fasting during four hours after the injection. In some experiments the blood was collected in centrifuge tubes and allowed to coagulate, after which the serum was removed by centrifuging at 2500 revolutions a minute. In other experiments the blood was heparinized by the addition of 0.1 ml. of a 5 per cent solution of heparin per 15 ml. of blood. The plasma and red blood corpuscles were separated by centrifuging as previously described.

The total esterase in the serum, plasma, blood corpuscles

and whole blood was estimated at a pH of 7.4 and 8.8 without the addition of calcium oleate and at a pH of 8.8 with the addition of the oleate. The esterases resistant to atoxyl and quinine were determined under the same conditions, and likewise the esterase resistant to both quinine and atoxyl. The resistance of serum esterase to atoxyl and quinine was then titrated. After it was found that the pancreatic lipase in serum could be estimated without the normal serum esterase having any mentionable effect on the result, the relationship between the amount of pancreatic lipase in serum and the reaction constant was examined.

Results (tables 2 and 3).—The total esterase activity in normal

Table 2.

Comparison of the Blood Esterase Activity Before (I) and 3 Hours After (II) Injection of 10 mg. of Morphine Hydrochloride Subcutaneously and 80 Clinical Units of Secretin Intravenously.

Addition of	1 Ml plasma			1 Ml. red blood corpuscles			1 Ml. blood		
	I	II	II—I	I	II	II—I	I	II	II—I
I 1 Ml. 4 M buffer pH 8.8 + 1 Ml. 0.5 % sodium oleate + 1 Ml. 0.25 % calc. chlor.									
1 Ml. H <sub>2</sub> O .....	50	157	107	40.8	47.8	+7			
1 Ml. 0.2 % atoxyl <sup>1</sup> ..	15	124	109	32.1	36.3	+4.2	18	51	33
1 Ml. 0.5 % quinine <sup>2</sup>	4—3 <sup>3</sup>	83—30 <sup>3</sup>		27.2	28.7	+1.5			
atoxyl + quinine as above .....	2	97—77 <sup>3</sup>							
II 1 Ml. 4 M buffer pH 8.8 + 2 Ml. H <sub>2</sub> O.									
1 Ml. H <sub>2</sub> O .....	54	51	—3	44.3	39	—5.3			
1 Ml. 0.2 % atoxyl <sup>1</sup> ..	14	18	5	29.3	21	—8.3			
1 Ml. 0.5 % quinine <sup>2</sup>	3	3	0	24.3	20.8	—3.5			
atoxyl + quinine ..	2	2	0	27.7	25.3	—2.4			
III 1 Ml. 1/3 M buffer Ph 7.4 + 2 Ml. H <sub>2</sub> O.									
1 Ml. H <sub>2</sub> O .....	24	25	1	28.8	23	—5.8			
1 Ml. 0.2 % atoxyl <sup>1</sup> ..	2.8	3.5	0.7	19.7	19.8	+0.1			
1 Ml. 0.5 % quinine <sup>2</sup>	1.2	1.7	0.5	18.2	18.7	+0.5	10	9	—1
atoxyl + quinine ..	0.5	0.7	0.2	21	18.5	—2.5			

<sup>1</sup> Added to plasma, red blood corpuscles or whole blood 30 min. before the hydrolysis.

<sup>2</sup> Added to the tributyrin before the hydrolysis.

<sup>3</sup> Increasing inhibition during the course of the hydrolysis.



plasma (plasma I) was about one hundred per cent greater at a pH of 8.8 than of 7.4. The addition of calcium oleate did not affect the activity.

The addition of 2 mg of atoxyl to the plasma half an hour before the determination inhibited the activity about 75 per cent at pH's of both 7.4 and 8.8, both when calcium oleate was added and when it was not.

The addition of 5 mg of quinine direct to the substrate under the same conditions caused an inhibition of about 95 per cent. The addition of both atoxyl and quinine caused slightly greater inhibition.

The esterase activity in the plasma obtained three hours after the injection of morphine and secretin (plasma II) was not significantly

Table 3.

Comparison of the Blood Esterase Activity Before (I) and 3 Hours After (II) Injection of 10 mg. of Morphine Hydrochloride Subcutaneously and 80 Clinical Units of Secretin Intravenously.

Addition of	1 Ml. serum			1 Ml. plasma			1 Ml. blood		
	I	II	II—I	I	II	II—I	I	II	II—I
I 1 Ml. 4 M buffer pH 8.8 + 1 Ml. 0.5% sodium oleate + 1 Ml. 0.25% calc. chlor.									
1 Ml. H <sub>2</sub> O .....	45.0	127	+82	37.1	123	+ 96	35.5	71.0	35.5
1 Ml. 0.2% atoxyl <sup>1</sup>	14.5	105	+90	11.4	114	+103	17.7	49.9	32.2
1 Ml. quinine 0.5% <sup>2</sup>	3.1	80—25 <sup>3</sup>		2.3	74—52 <sup>3</sup>		14.9	37—23 <sup>3</sup>	
atoxyl + quinine as above .....	1.8	61—50 <sup>3</sup>		3.2	43—33 <sup>3</sup>		14.6	35—29 <sup>3</sup>	
II 1 Ml. 4 M buffer pH 8.8 + 2 Ml. H <sub>2</sub> O.									
1 Ml. H <sub>2</sub> O .....	48.6	45.2	—3.4	43.9	45.6	+1.7			
1 Ml. 0.2% atoxyl <sup>1</sup>	12.5	13.9	+1.5	10.8	11.2	+0.4			
1 Ml. 0.5% quinine <sup>2</sup>	2.6	3.2	+0.6	2.75	2.62	+0.1			
atoxyl + quinine	2.1	2.2	+0.1	1.89	1.71	—0.2			
III 1 Ml. 1/3 M buffer pH 7.4 + 2 Ml. H <sub>2</sub> O.									
1 Ml. H <sub>2</sub> O .....	17.9	24.3	+6.4	22.3	23.7	+1.4	20.3	23.4	+3.1
1 Ml. 0.2% atoxyl <sup>1</sup>	2.9	3.6	+0.7						
1 Ml. 0.5% quinine <sup>2</sup>	1.2	1.4	+0.2				9.4	8.6	—0.8
atoxyl + quinine	0.4	0.8	+0.4						

<sup>1</sup> Added to serum, plasma or whole blood 30 min. before the hydrolysis.

<sup>2</sup> Added to the tributyrin before the hydrolysis.

<sup>3</sup> Increasing inhibition during the course of the hydrolysis.

elevated compared with the activity in plasma I, in the experiments where calcium oleate was omitted.

After the addition of calcium oleate, the activity in plasma II, both of the total esterase and of the esterase resistant to atoxyl, quinine and to both these poisons, rose greatly. Thus an esterase had entered this plasma, which could not be definitely demonstrated without the addition of calcium oleate, but which became highly active when it was added.

The total esterase activity in plasma II was about three times greater after the addition of calcium oleate than in plasma I. The activity of the atoxyl-resistant esterase was about eight times greater than in plasma I.

The atoxyl-resistant esterase rose the same number of units as the total esterase. Thus the newly entered esterase was completely insensitive to the amount of atoxyl used.

After the addition of quinine the value for the reaction constant for plasma II fell rapidly as the hydrolysis progressed. The new esterase was thus inhibited by quinine, but the inhibition was not instantaneous as in the case of the esterase in normal plasma.

*The esterase activity of the serum* was similar to that of the plasma under all the experimental conditions.

The determination of esterase in the blood corpuscles is more subject to error than estimations in the plasma or serum. After centrifugation and removal of the plasma, the blood corpuscles form a thick porridge which is difficult to pipet exactly. This porridge contains a small amount of plasma. Consideration was given to these factors when the results were judged.

The total esterase activity of the red blood corpuscles in specimen I was slightly less than that of the serum at a pH of 8.8, and at pH 7.4 slightly greater. It was about 30 per cent greater at a pH of 8.8 than of 7.4. The addition of calcium oleate did not change the activity. The blood corpuscle esterase was only slightly inhibited by the amounts of atoxyl and quinine used in the foregoing experiments.

The esterase activity in the blood corpuscles from specimen II did not differ significantly under any experimental condition from the activity in specimen I. The new esterase was thus not absorbed or adsorbed to a measurable degree by the blood corpuscles.

Table 4.

*Influence of Atoxyl on the Esterase Activity.*

I sample taken before, II 3 hours after injection of morphine and secretin.  
 4 M buffer pH 8.8 + 1 Ml. 0.5 % sodium oleate + 1 Ml. 0.25 % calcium chloride.

Experiment	Ml. serum (s.) or plasma (p.)	Addition of	Min. before hydrolysis	Esterase activity		
				I	II	II—I
1	1 p.		30	50	157	107
		1 Ml. 0.2 % atoxyl	30	15	124	109
		5 Ml. 0.2 % atoxyl	60	4.5	111	107
		1 Ml. 0.2% atoxyl + 4 Ml. H <sub>2</sub> O	30	8.8	77	68
		3 Ml. 0.2% atoxyl + 2 Ml. H <sub>2</sub> O	30	3.6		
2	0.5 s.	5 Ml. 0.2 % atoxyl	30	2.3	75	73
		5 Ml. 0.4 % atoxyl	16	1.8		
			30	1.7	72	70
		2 Ml. 0.4 % atoxyl	15	3.5		
			30	3.8		
3	0.5 s.	1 Ml. 0.2 % atoxyl	30	9.3	32.2	23
		1 Ml. 2.0 % atoxyl	30	1.7	28.9	27

The esterase activity in the whole blood of specimen I was the sum of the activity in the plasma and in the red blood corpuscles. In specimen II it was lower. This condition will be discussed later (p. 28).

*Titration of resistance to atoxyl and quinine.* — Like other authors, I found that the amount of atoxyl recommended by Rona and his co-workers did not cause complete inhibition of the normal serum esterase. I therefore made a few experiments to learn the influence of the time of inhibition, the concentration of atoxyl and the amount of atoxyl on the esterase activity (table 4). The determinations were made with addition of calcium oleate. The inhibition reached its maximum in fifteen minutes. Changes in the concentration of atoxyl, produced by adding different amounts of water during the reaction between atoxyl and serum, had no significant effect on the inhibition. Increase of the atoxyl to ten times the amount prescribed by Rona and his co-workers gave a value about five times lower for the normal esterase, but did not affect the reaction constant for the esterase in specimen II which

Table 5. Influence of Quinine on the Esterase Activity.

I sample taken before, II 3 hours after injection of morphine and secretin.  
1 ml. 4 M buffer pH 8.8 + 1 Ml. 0.5 % sodium oleate + 1 Ml. 0.25 % calcium chloride. 0.5 Ml. plasma.

Addition of	Min. before hydrolysis	Digestion time, min.	Esterase activity	
			I	II
5 Ml. HO <sub>2</sub> .....	0	4—12	50	157
0.5 Ml. 0.5 % quinine + 4.5 Ml. H <sub>2</sub> O to the tributyrin .....	2	5.25 8.75 31 61 131	7.0 6.7 4.7	97 78
0.5 Ml. 0.5 % quinine + 4.5 Ml. H <sub>2</sub> O to the plasma .....	30	7.25 10.2 31 62 121	7.3 6.5 5.2	80 66
1 Ml. 0.5 % quinine + 4 Ml. H <sub>2</sub> O to the tributyrin .....	2	7.5 11.75 16.75 35 59 125	5.4 5.4 4.4	54 42 33
1 Ml. 0.5 % quinine + 4 Ml. H <sub>2</sub> O to the plasma .....	30	7.2 16.7 35.5 32.5 60.0 124	5.5 5.7 3.5	45 28 13
2 Ml. 0.5 % quinine + 3 Ml. H <sub>2</sub> O to the tributyrin .....	2	9.0 12.25 15.75 35 66.25 126.5	2.5 2.4 2.6	32 33 31
2 Ml. 0.5 % quinine + 3 Ml. H <sub>2</sub> O to the plasma .....	30	6.25 15.25 12.75 34 62 118	3.8 2.9 2.4	27 26 25
2 Ml. 0.5 % quinine + 3 Ml. H <sub>2</sub> O to the plasma .....	65	8.2 21.25 36.75 30.0 52.5	2.7 2.6	15 14 11

Table 6.

*The Relation Between Different Amounts of Serum and the Reaction Constant (C). Serum 3 hours after the injection of morphine and secretin. Addition of 5 Ml. 0.4 % atoxyl to serum 30 min. before hydrolysis. 1 Ml. 4 M buffer pH 8.8 + 1 Ml. 0.5 % sodium oleate + 1 Ml. 0.25 % calcium chloride. 1 Ml. serum dilution.*

Dilution, times	Digestion time, min.	C × 1000	C times dilution × 1000
1	4.50	122	111
	7.33	100	
2	5.42	70	139
	6.17	73	
	6.25	66	
	8.00	73	
	8.67	66	
4	6.00	32	139
	11.25	34	
	21.00	38	
8	11.00	15.3	119
	21.00	14.9	
	41.00	14.6	
16	21.5	3.5	53
	41.0	3.1	
	81.25	3.4	
	116.00	2.1	
32	40.00	1.8 1.8	58
	82.00	1.2	
	122.00	1.0	
	250.00	0.8	

probably came from the pancreas. The inhibition was not directly proportional to the logarithm for the amount of atoxyl, as in Rona's experiments. Instead the logarithm for the inhibition was approximately proportional to the logarithm for the amount of atoxyl. Sufficient inhibition for practical purposes was obtained with 2 mg of atoxyl. Judging from the inhibition curve, complete inhibition is only obtained with large amounts of atoxyl.

In order to compare the resistance to quinine of normal serum esterase with that of the esterase which entered the serum after the injection of secretin and morphine, different times of inhibition and different amounts of quinine were tested in the same way.

Table 7.

*The Relation Between Different Amounts of Pancreatic Lipase in Serum and the Reaction Constant (C).*

Serum I before, serum II 3 hours after the injection of morphine and secretin. Serum II mixed with different amounts of serum I in order to make the concentration of lipase II independent of the amount of serum protein. Addition of 5 ml. 0.4 % atoxyl 30 min. before hydrolysis. 1 ml. 4 M buffer pH 8.8 + 1 ml. 0.5 % sodium oleate + 1 ml. 0.5 % calcium chloride.

Serum I			Serum I + Serum II			Lipase II-Lipase I	
Dilution times	Digestion time, min.	C × 1000	Dilution of lipase II, times	Digestion time, min.	C × 1000	C × 1000	C times dilution × 1.000
2	66	1.9	2	5.42	70	69.5	67.8
2	150	1.7		6.17	73		
2	153	1.5		6.25	66		
				8.00	73		
				8.67	66		
2		1.7	4	6.00	32.0	34.4	32.7
				10.50	36.8		
2		1.7	8	12.16	18.5	18.1	16.4
				21.25	19.0		
				41.00	16.8		
2		1.7	16	21.00	8.7	8.5	6.8
				41.00	8.3		
				84.25	6.6		
2		1.7	32	39.50	5.4	5.4	3.7
				87.00	4.2		
				121.00	3.4		
				140.00	3.3		
1			16	21.00	3.6	3.7	
				42.75	3.7		
4		0.85	16	21.00	7.4	8.1	7.2
				42.25	8.7		
8		0.425	16	22.25	8.6	8.3	7.9
				41.00	8.0		

as in the case of atoxyl (table 5). The normal serum esterase was inhibited immediately. The inhibition was equally great, whether the quinine was added to the tributyrin or to the serum. It increased with rising doses of quinine from about 90 per cent on the addition of 2.5 mg to 95 per cent on the addition of 10 mg.

Table 8.

*Esterase Activity of Normal Serum to which Pancreatic Juice has Been Added Under Different Conditions.*

Experiment	Addition of	1 Ml. inactivated serum	1 Ml. inactivated serum + pancreatic juice	1 Ml. active serum	1 Ml. active serum + pancreatic juice	1 Ml. active serum + pancreatic juice — active serum
1 <sup>1</sup>	1 Ml. 4 M buffer pH 8.8 + 1 Ml. 0.5 % sodium oleate + 1 Ml. 0.25 % calcium oleate.					
	1 Ml. H <sub>2</sub> O					
	30 min. before hydrolysis	0	21.6	10.1	38.1	+28.0
	1 Ml. 0.2 % atoxyl					
	30 min. before hydrolysis	0	19.0	3.4	32.8	+29.4
	1 Ml. 2 % atoxyl					
	30 min. before hydrolysis	0	20.4	0.8	29.5	+28.7
	1 Ml. 4 M buffer pH 8.8 + 2 Ml. H <sub>2</sub> O.					
	1 Ml. H <sub>2</sub> O					
	30 min. before hydrolysis	0	0.4	10.5	9.9	— 0.6
	1 Ml. 2 % atoxyl					
	30 min. before hydrolysis	0	0.4	0.7	0.8	+ 0.1
2	1 Ml. 4 M buffer pH 8.8 + 1 Ml. 0.5 % sodium oleate + 1 Ml. 0.25 % calcium oleate.					
	1 Ml. H <sub>2</sub> O					
	0 min. before hydrolysis <sup>2</sup>			50	111	+61
	1 Ml. 0.2 % atoxyl					
	30 min. before hydrolysis <sup>3</sup>			16	78	+62
	1 Ml. 4 M buffer pH 8.8 + 2 Ml. H <sub>2</sub> O.					
	1 Ml. H <sub>2</sub> O					
	0 min. before hydrolysis <sup>2</sup>			54	55	+ 1
	1 Ml. 0.2 % atoxyl					
	30 min. before hydrolysis <sup>3</sup>			13	17	+ 4

<sup>1</sup> 0.4 Ml. of a mixture of equal parts of pancreatic juice and glycerin added to 38 Ml. serum 2 days before the experiments.

<sup>2</sup> 0.01 Ml. of a mixture of equal parts of pancreatic juice and glycerin added directly to the digestion mixture.

<sup>3</sup> 0.01 Ml. of a mixture of equal parts of pancreatic juice and glycerin added to 1 Ml. of serum 2 min. before addition of atoxyl.

The inhibition of the esterase which entered the serum after morphine and secretin was less when the quinine was added to the tributyrin than when it was added to serum. The inhibition in-

Table 9.

*Increase of Amylase<sup>1</sup> and Pancreatic Esterase in Serum After Subcutaneous Injection of 10 mg. Morphine and Intravenous Injection of 80 Clinical Units of Secretin.*

Case	Enzyme	Hours after injection						
		0	1	2	4	8	16	24
1.	Amylase	33		68				
	Esterase	2.6		13				
2.	Amylase	34		54				
	Esterase	2.2		11				
3.	Amylase	31		33	34			
	Esterase	2.6		1.6	4.4			
4.	Amylase	32	96	172	224	164	57	43
	Esterase	1.5	48	44	50	19	8.8	5.4
5.	Amylase	23	46	54	62	54	34	28
	Esterase	4		11	10	6.8	3.2	0
6.	Amylase	22		55	65	49	23	
	Esterase	3.6			14	6.2	1.6	
7.	Amylase	43	66	74	66	45	45	
	Esterase	4.8	11	7.6	5.6	6.4	6.4	
8.	Amylase	25	64	97	107	83	55	47
	Esterase	3.4	33	58	54	24	8	5.5
9.	Amylase	23	36	204	508	392	142	89
	Esterase	2.6	16	164	201	69	5.9	4.1
10.	Amylase	30	66	92	113	91	51	38
	Esterase	2.9	26	35	17	7.8	5.9	4.9
11.	Amylase	52	82	132	142	112	67	55
	Esterase	2.6	18	33	26	18	7.1	4.7

<sup>1</sup> Nørby units (23) × 10000.

creased with the length of time the poisoning proceeded. Reckoned in per cent, it was much less than in the case of normal serum esterase, amounting to about 55 per cent when 2.5 mg of quinine were added to the tributyrin and to about 80 per cent when 10 mg were added.

*Connection Between the Amount of Esterase and the Reaction Constant.* — Serum obtained after the injection of morphine and secretin (serum II) was diluted in a geometric series with distilled water and poisoned with atoxyl. Calcium oleate was added to the tributyrin and the reaction constant (C) determined after varying



periods of digestion (table 6). In these experiments, as in others, a fall in the reaction constant was observed as the reaction progressed. This fall was so slight up to forty-five minutes that it required no consideration. Only values obtained within this time will be discussed in the following.

When the serum was diluted to one-half or one-quarter the product of  $C \times$  the dilution was constant, i.e.,  $C$  was reversely proportional to the dilution. When the serum was undiluted, the product of  $C \times$  the dilution was lower, and when it was diluted to onesixteenth or more, it did not amount to half the values for the serum diluted to one-half or one-quarter.

There was a possibility that the changes in the protein concentration during the hydrolysis influenced the rate of hydrolysis. Willstätter and Memmen (41) have shown that egg albumin added to pancreatic lipase activated with calcium oleate causes further activation which reaches its maximum in a certain region of the protein concentration.

To investigate this possibility, serum II was mixed with varying amounts of serum I in such a manner that the protein concentration was kept constant (table 7). The reaction constant for the new esterase present in serum II was calculated from the difference between the reaction constant of the mixture and the reaction constant of the esterase in serum I. Under these conditions the reaction constant for all the amounts of esterase II used was reversely proportional to the amount of esterase, within the limits of error of the method. Special experiments showed that the variations in protein concentration which occur in serum dilutions one to two up to one to eight are of no importance. Thus, in order to obtain a suitable drop difference, the serum can be diluted within these limits without the esterase values being affected.

#### *The Esterase Activity in Serum to Which Pancreatic Juice has been Added.*

It was shown in the foregoing section that a new esterase with new properties appears in serum after the injection of morphine and secretin. That this esterase is identical or closely related to pancreatic lipase appears from experiments in which small amounts of pancreatic juice were added to serum (table 8).

The esterase activity in this serum increased greatly after the addition of calcium oleate. It increased the same amount when atoxyl was added to the serum. The pancreatic lipase was thus fully resistant to atoxyl. When no calcium oleate was added, no definite increase in the activity of the serum esterase was observed after the addition of pancreatic juice.

The esterase activity of pancreatic juice was determined after the addition of serum which had been inactivated by heating three hours at 55 to 60 C. The increase in activity in active normal serum plus pancreatic juice was about 25 per cent greater than corresponded to the amount of esterase determined in this manner. The reason for this difference is still obscure.

#### *Comparison Between the Increase of Amylase and Pancreatic Esterase.*

The increase of pancreatic esterase in the blood after the injection of morphine and secretin was compared in eleven cases with the increase in amylase under the same conditions (table 9). The esterase determinations were done with calcium oleate added at a pH of 8.8 with 0.5 Ml. of serum, poisoned with 1 Ml. of a 2 per cent atoxyl solution for thirty minutes. All the cases which showed an increase in amylase also showed an increase in esterase. The rise in esterase was generally much greater in proportion to that of the amylase. It varied between 0.7 to 76 times the initial value for esterase and 0.1 to 21 times the initial value for amylase. The esterase reached its maximum after about two hours, the amylase about two hours later. The amylase and esterase reached their normal values at about the same time. The greater the rise, the longer it lasted. In six cases it lasted more than twenty-four hours.

#### **Discussion.**

Plasma, serum and red blood corpuscles contain normal esterases. In my experiments the esterase activity was alike in plasma and serum under a series of varying conditions. It is probable, therefore, that they contained the same sort of esterase and that it was not chemically or physically bound to the fibrin.

The serum of different persons behaves similarly under a series

of different conditions. Different sera are inhibited to the same extent and according to the same laws by atoxyl and quinine. The relation between the methyl butyrate, tributyrine and acetylcholine splitting power of human serum is constant in different healthy subjects under different conditions and in different diseases outside the pancreas. It is also constant when serum is cataphoresed or poisoned with quinine, atoxyl and physostigmine. My experiment also shows that, unlike pancreatic lipase, serum esterase is not activated by calcium oleate. All these facts indicate that the composition of normal serum and plasma esterase is constant or almost so, i.e., the normal serum or plasma esterase seems to be a chemical individual. The serum esterase is well differentiated from the pancreatic lipase.

The degree of resistance of normal serum to atoxyl is of importance for the differentiation of serum esterase from pancreatic lipase. According to Rona and collaborators, the inhibition of serum esterase with atoxyl follows the formula  $\frac{C_A - C_B}{\log B - \log A} = C$ , in which  $C_A$  and  $C_B$  represent the reaction constants and A and B the concentrations of poison. From this formula Rona calculated the smallest amount of atoxyl which caused complete inhibition of serum esterase and found it to be 0.15 mg if the total volume of the substrate (tributyrin) was 35 Ml. and the pH about 7.6. For clinical use they recommended an amount of 2 mg per 3 Ml. serum and 55 Ml. of substrate. It is evident from a great number of clinical studies that the esterase activity of serum so poisoned is not completely inhibited, amounting to about one-sixth of the original. My experiments show that the inhibition is still less when the determinations are done at pH 8.8. Under these conditions the inhibition does not follow the formula of Rona and collaborators. Submaximal inhibition is not reached until 20 mg of atoxyl are added and total inhibition probably only with very great amounts.

The esterase of the red blood corpuscles behaves quite differently from the serum and plasma esterase and also from the pancreatic lipase. In contradistinction to serum and plasma esterase, it is very resistant to atoxyl and quinine. It differs from pancreatic lipase in its resistance to quinine and in its inability to be activated by calcium oleate.

The pancreatic lipase splits tributyrin slowly if no activators

are added. It is activated at least fifty times by the addition of adequate amounts of calcium oleate.

It is completely resistant to doses of atoxyl which cause submaximal inhibition of serum esterase. It is inhibited by quinine but not to the same degree as serum esterase. The inhibition proceeds slowly unlike the inhibition of serum esterase which takes place instantaneously. When quinine is added to the substrate, therefore, the reaction constant falls continuously with increasing time of digestion.

When pancreatic lipase and serum esterase are mixed *in vitro*, they both retain their properties and can each be determined separately. The same is the case if lipase diffuses out from the pancreas *in vivo*.

When serum esterase and pancreatic lipase are mixed, the serum esterase is determined without the addition of calcium oleate. The difference between the total esterase activity and the activity which persists after submaximal inhibition gives the activity of the serum esterase to within a small per cent of error. The activity of the atoxyl-resistant esterase is usually so small that it can be disregarded, as the activity of pancreatic lipase is extremely slight if it is determined without the addition of activators.

The pancreatic lipase is determined after the addition of calcium oleate and during submaximal inhibition with atoxyl. The values thus obtained are some per cent too high due to the action of small amounts of normal esterase which are not inhibited by atoxyl. This amount may be determined without the addition of calcium oleate and then subtracted.

Theoretically pancreatic lipase can be converted to serum esterase and vice versa by changes in the equilibria

$$\frac{\text{agon} \cdot \text{pancreatic lipase pheron}}{\text{pancreatic lipase}} = C \text{ pancreatic lipase}$$

$$\frac{\text{agon} \cdot \text{serum esterase pheron}}{\text{serum esterase}} = C \text{ serum esterase}$$

The fact that pancreatic lipase and serum esterase retain their activity and other properties when they are mixed both *in vitro* and *in vivo* (the titer of serum esterase as a rule does not change when pancreatic lipase diffuses out) indicates that such a conversion, if it occurs, does so to a minor extent.

When pancreatic lipase is diffused out into the blood, it is not

absorbed or adsorbed by the red blood corpuscles. Thus it is unlikely that pancreatic lipase can be converted to red cell esterase, *in vivo*. Hemolyzed red blood corpuscles inhibit pancreatic lipase, making it impossible to estimate the lipase in whole blood. This inhibiting effect may be due to the pancreatic lipase being converted to red cell esterase or to the hemoglobin inhibiting pancreatic lipase like other oxidizing substances.

### Summary.

1) Normal serum or plasma esterase is inactivated to about 95 per cent by the addition of 1 Ml. of a 2 per cent solution of atoxyl per milliliter of serum or plasma, a tenfold greater amount of atoxyl than used by other authors. It is not activated by calcium oleate.

2) The esterase of the red blood corpuscles is not activated by calcium oleate.

3) A new technic was used to produce delivery of pancreatic lipase into the blood of humans. The pancreatic secretion was stimulated with secretin at the same time as Oddi's sphincter was made to contract with morphine. This caused the signs of mild acute pancreatic disease, especially in cholecystectomized persons. In addition to an increase of lipase, the blood also showed an increase of amylase.

4) Pancreatic lipase in serum and pancreatic juice is completely resistant to the amounts of atoxyl which cause submaximal inhibition of normal serum esterase. It is relatively resistant to quinine as well. Its activity is increased at least fiftyfold by the addition of calcium oleate at a pH of 8.8. It is not absorbed or adsorbed by the red blood corpuscles.

5) Moderate amounts of pancreatic lipase in serum could not be demonstrated without activation. Under such conditions the esterase activity is due only to normal serum esterase.

6) Pancreatic lipase in serum can be determined separately from the serum esterase if the latter is inhibited submaximally with atoxyl and the pancreatic lipase is activated with calcium oleate.

7) If the pancreatic lipase is determined in this way, the rise in lipase under the conditions given in 3) is proportionally much greater than that of the serum amylase.

# Bibliography.

1. Ammon, R.: Esterasen, Nord-Weidenhagen's Handbuch der Enzymologie. Akad. Verlagsgesellschaft Becker & Erler Kom. Ges. Leipzig, 350; I, 1940. — 2. Beckman, T.: Contributions au diagnostic des panaréatites chirurgicales, Acta Chir. Scandinav. 78; 1936, suppl. 44. — 3. Bernhard, F.: Cit. Schmitt K. Arch. klin. Med. 174; 523, 1933. — 4. Birath, G.: Om metodiken vid bestämning av chininresistent serumlipaser enl. Rona, Nordisk Med. Tidskr. 15; 926, 1938. — 5. Broekmeyer, J.: Über die Wirkung des Cocains und des Strychnins auf einige Organlipasen, Klin. Wchnschr. 34; 1526, 1924. — 6. Cherry, I. S. Crandall, L. A.: The Specificity of Pancreatic Lipase: its Appearance in the Blood after Pancreatic Injury, Am. J. Physiol. 100; 266, 1932. — 7. Comfort, M. W., Osterberg, H. E.: Lipase and Esterase in Blood Serum. Their Diagnostic Value in Pancreatic Disease, Proc. Staff Mayo Clin. 9; 250, 1934. — 8. Davidsohn, H.: Über die Abhängigkeit der Lipase von der Wasserstoffionkonzentration, Biochem. Ztschr. 49; 249, 1913. — 9. Engelhart, E., Loewi, O.: Fermentative Acetylcholinspaltung im Blut und ihre Hemmung durch Physostigmin, Arch. f. exper. Path. u. Pharmacol. 150; 1, 1930. — 10. Fiessinger, N., Albeaux-Fernet, M., Gajdos, A.: De l'influence de la pancréatectomie chez le Chien sur la teneur du sang en lipase, Compt. rend. Soc. de biol. 112; 549, 1933. — 11. Fiessinger, N., Albeaux-Fernet, M., Gajdos, A.: Contribution à l'étude des lipases du sérum, Annal. d. Med. 34; 101, 1933. — 12. Gradnauer, A.: Über den Serumlipasetiter bei der Tuberculose des Kindes, Beitr. z. Klin. d. Tuberculose 77; 725, 1931. — 13. Grassberger, A.: Diastase und Lipasewerte im Blut bei operativ gesetzten Pankreasverletzungen, Mitteil. a. d. Grenzgeb. d. Med. u. Chir. 41; 1, 1928. — 14. Grassberger, A.: Fermentuntersuchungen im Blut bei Pankreaserkrankungen mit besonderer Berücksichtigung des in das Pankreas penetrierenden Magen-Duodenalulcus, Deutsche Ztschr. f. Chir. 210; 293, 1928. — 15. Hangleiter, H., Reuter, A.: Über den Lipasegehalt des Blutserums, Ztschr. f. d. gesamt. exper. Med. 107; 355, 1940. — 16. Hendricksson, W. F.: A Study of the Musculature of the Entire Extrahepatic Biliary System, Including That of the Duodenal Portion of the Common Bile Duct and the Sphincter. Bull. Johns Hopkins Hosp. 9; 221, 1898. — 17. Hiruma, K.: Zur Frage der Herkunft der Lipase im Blut, Biochem. Ztschr. 139; 336, 1923. — 18. Johnson, T. A., Bockus, H. L.: Diagnostic Significance of Determinations of Serum Lipase, Arch. Int. Med. 66; 62, 1940. — 19. Jedlička, V., Kreisinger, V.: Zur Frage des Nachweises der pankreatischen Lipase im Serum bei Pankreaserkrankungen, Ztschr. f. d. gesamt. exper. Med. 47; 513, 1925. — 20. Kitakoji, Y.: Über den Einfluss von Nervengiften auf die Funktionen der Gallenblase und des Oddischen Muskels, Nagoya J.M. Se. 5; 24, 1930. — 21. Kraut, H., v. Pantshenko-Jurewicz, W.: Über Struktur und Eigenschaften der Esterasen, Biochem. Ztschr. 275; 114, 1934/35. — 22. Lagerlöf, H.: Pancreatic Function and Pancreatic Disease Studied by Means of Secretin, Acta med. Scand. Suppl.

- 128, 1942 & Mac Millan Company, New York, 1942. — 23. Lasch, C.H.: Der Nachweis atoxylresistenten Lipasen im Serum und ihre Bedeutung für die Pankreasdiagnostik, *Arch. klin. Chir.* 150; 272, 1928. — 24. Plattner, F.: Der Nachweis des Vagusstoffes beim Säugetier, *Arch. f. d. ges. Physiol.* 214; 112, 1926. — 25. Popper, H. L., Scholl, R.: Verwertbarkeit der Lipasebestimmung zur Diagnose der Pancreatitis, *Med. Klin.* 30; 335, 1934. — 26. Rona, P., Bach, E.: Beiträge zum Studium der Giftwirkung. Über die Wirkung des Atoxyls auf Serumlipase, *Biochem. Ztschr.* 111; 166, 1920. — 27. Rona, P., Ebsen, J.: Weitere Beiträge zur Kenntnis der Ester-spaltung im Blute, *Biochem. Ztschr.* 39; 21, 1912. — 28. Rona, P., Michacalis, L.: Über Ester- und Fettspaltung im Blute und im Serum, *Biochem. Ztschr.* 32; 345, 1911. — 29. Rona, P., Pavlović, R.: Beiträge zum Studium der Giftwirkungen. Über die Wirkung des Chinins und des Atoxyls auf Leberlipase, *Biochem. Ztschr.* 130; 225, 1922. — 30. Rona, P., Pavlović, R.: Über die Wirkung des Chinins und des Atoxyls auf Pankreaslipase, *Biochem. Ztschr.* 134; 108, 1922—23. — 31. Rona, P., Petow, H.: Weitere Untersuchungen über die Giftempfindlichkeit von Lipasen verschiedener Herkunft, *Biochem. Ztschr.* 146; 144, 1924. — 32. Rona, P., Petow, H., Schreiber, H.: Eine Methode zum Nachweis blutfremder Fermente im Serum, *Klin. Wchnschr.* 1; 2366, 1922. — 33. Schmitt, K.: Der Wert der Lipasebestimmung im Blutserum für die Diagnose der akuten und chronischen Pankreaserkrankungen, *Arch. f. klin. Chir.* 174; 510, 1933. — 34. Simon, H.: Über rote Blutkörperchen und Serumlipase, *Ztschr. f. d. gesamt. exper. Med.* 39; 407, 1924. — 35. Simon, H.: Über die Bedeutung des Nachweises atoxylresistenter Lipase im Serum bei Pankreaserkrankungen und Anaemia Perniciosa, *Klin. Wchnschr.* 48; 2295, 1925. — 36. Traube, J.: Capillaranalyse, Abderhaldens Handbuch der Biologischen Arbeitsmethoden, Abt. III, Physikal.-chem. Methoden, Teil A I, p. 869. — 37. Virtanen, A. I., Suomalainen, P.: Untersuchungen über die Lipasen im Tierorganismus, *Ztschr. f. physiol. Chem.* 219; I, 1933. — 38. Wahlquist, B.: On the Esterase Activity of Human Blood Plasma, *Scand. Arch. f. Physiol.* 72—73; 133, 1935—36. — 39. Walters, W., Mc Cowan, J. M., Butsch, N. L.: The Pathologic Physiology of the Common Bile Duct. Its Relation to Biliary Colic, *J. A. M. A.* 109; 1591, 1937. — 40. Willstätter, R., Waldsehnidt-Leitz, E., Memmen, F.: Bestimmung der Pankreatischen Fettspaltung, *Ztschr. f. physiol. Chem.* 125—126; 93, 1922—23. — 41. Willstätter, R., Memmen, F.: Zur stalagmometrischen Bestimmung der lipatischen Tributyrinhydrolyse, *Ztschr. f. physiol. Chem.* 129; 1, 1923. — 42. Willstätter, R., Memmen, F.: Hoppe-Seylers Z. 216; 138, 1924. *Git. Nord & Weidenhagens Handbuch der Enzymologie. Akad. Verlagsgesellschaft Becker & Erler Kom. Ges., Leipzig 1940.* — 43. Zorn, B.: Über fettspaltende Blut- und Harnfermente und ihre Beziehungen zu physiologischen und pathologischen Vorgängen, *Fermentforschung, Neue Folge* 8, 15; 397, 1938.
-

From the Blegdamshospital, (Chief: Professor Dr. H. C. A. Lassen) and the Pathology Department, Norre Hospital and De Gamles By (Chief: Prosector Dr. O. Wanschier), Copenhagen.

## The Histopathology of the Liver in Infectious Mononucleosis Complicated by Jaundice, Investigated by Aspiration Biopsy.

By

JENS BANG and O. WANSCHER.

(Submitted for publication October 27, 1944).

---

Infectious mononucleosis is occasionally complicated by jaundice. Stig Thomsen found jaundice in 3.8 % of his material (total 549 patients), Øllgaard in 2 % (total 210). Jaundice may occur both with and without enlargement of the liver, its intensity is on the average not particularly great, and its duration rather short. The time of the disease at which the jaundice appears varies; most frequently the jaundice develops in the course of the disease, but occasionally it may be the first symptom (Nyfeldt, Stig Thomsen); in a few instances there may be no angina and enlargement of the glands, and the blood picture alone supplies the diagnosis.

Opinions differ as to the cause of jaundice in mononucleosis. Some authors (Nyfeldt; Glanzmann; Schwartz) assume an acute hepatitis to be responsible, an assumption which is supported by the circumstance that urobilin in the urine frequently is observed during the febrile stage of the disease, even though jaundice does not develop. Other authors (Mackey and Wakefield; Bueh; Stig Thomsen) assume the jaundice to be caused by biliary obstruction due to the pressure of swelled lymph-nodes in porta hepatis.



With the introduction of liver biopsy by Iversen and Roholm new possibilities present themselves for the investigation of the histopathology of the liver, and through investigations which have set out the microscopic anatomy both in infectious jaundice (Roholm and Iversen) and obstructive jaundice (Roholm and Krarup) a basis has been established for an elucidation of the problem: Does the infectious mononucleosis involve a hepatitis, i.e., an injury of the liver parenchyma due to the infection, or a simple obstructive jaundice due to the compression of the bile ducts by swelled lymph nodes?

In one case of mononucleosis van Beek and Haex have examined the liver with the aid of aspiration biopsy. Here it was not a case of jaundice, and the investigation had other purposes than elucidating the problem dealt with in the present paper, aiming as it did at the finding of evidence to support the idea of infectious mononucleosis as an affection of the reticulo-endothelial system. The microscopy showed a proliferation of monocytoïds among the liver cells which themselves showed mitoses. Some polymorphonuclear leucocytes and lymphocytes were also found in the portal tracts.

In the following we shall describe 4 cases of mononucleosis with jaundice which in the course of the last year-and-a-half have occurred at the Blegdams hospital. Aspiration biopsy of the liver has been carried out in accordance with the technique introduced by Iversen and Roholm.

#### *Case No. 1.*

21 years old mechanic, hospitalized 26. 11—17. 12. 1944.

Sick 8 days before admission, with fever, sore throat, gradual swelling of the cervical glands.

At the time of admission: Tonsillitis with membrane formation, enlarged cervical, axillary and inguinal glands.

*Blood:* White blood count 19.600 per mm<sup>3</sup>. Differential count: Stab cells 2 %, polymorphonuclears 25 %, abnormal mononuclears (of the type characteristic of infectious mononucleosis) 32 %, ordinary lymphocytes 35 %, monocytes 6 %.

*Paul-Bunnell's test:* Positive (titer 1024).

11th day of the disease: Incipient jaundice, bilirubin in the urine.

12th day: Pronounced jaundice, ieterus index (*Meulengracht*) 25.

15th day: *Liver biopsy.*

31st day: Jaundice disappeared, fauces clear, glandular swelling diminishing.

39th day: Patient dismissed in good health.

WR —, Widal —, Weil —.

*Histological description of liver tissue.*

Large beautiful specimen obtained, which, through an error, was not placed immediately in the fixative and therefore was somewhat dried up, making the histological investigation and the estimate of the findings a little difficult. The cells are medium-size, fairly uniform in size, with rather bright, granular and here and there slightly vacuolized protoplasm without fat content. The nuclei are medium-size, varying a little in size and in density of chromatin. A few cells have two nuclei. No certain mitoses. Scattered in the liver cells a little greenish pigment, and in the bile capillaries some small and fine biliary thrombi. The cell borders are not always sharp. The portal connective tissue is not increased in amount, but locally a little hyalinized with fine, dark streaks of cells. Everywhere in the portal tissue there is moderate infiltration of lymphocytes, a few plasma cells and some neutrophile and eosinophile leucocytes. This inflammatory infiltration is also seen to extend a little into the parenchyma outside the portal canals. No bile duct proliferation and no sign of tuberculosis or malignant tumor cells proliferation. The Kupffer cells are often swelled, and here and there in mitotic division. Since the tissue is fixed in formalin, no carmine staining for glycogen has been made.

*Microscopical diagnosis:* Hepatitis subacuta-subchron. in primis interstit. periport. medio grado. Hepatitis interstit. periport. seqv. levi grado. Icterus levi grado.

*Comment:* Clinically, hematologically and serologically a typical case of infectious mononucleosis. Jaundice from the 11th day. Liver biopsy on the 15th day shows mild parenchymatous and medium portal, subacute inflammation and mild jaundice as well as slight swelling of the Kupffer cells.

*Case No. 2.*

28 years old chauffeur, hospitalized 8. 5—22. 5. 1944.

Sick 6 days before admission, with fever and slight pains in the throat. 3 days before admission the urine was dark, but jaundice was not observed at home.

At the time of admission: Temperature 39.4° C. Jaundice in the sclerae. Slightly sore throat. No glandular swelling.

8th day of the disease: Icteric skin; bilirubin and urobilin in the urine, icterus index (*Meulengracht*) 28.

9th day: Tonsillitis with membrane formation; enlarged tender cervical glands, enlarged axillary and inguinal glands. Enlargement of the liver, but not of the spleen.

*Blood:* White blood count 14,000 per mm<sup>3</sup>. Differential count: Stab cells 7 %, polymorphonuclears 10 %, eosinophile 1 %, abnormal mononuclears (of the type characteristic of infectious mononucleosis) 55 %, ordinary lymphocytes 35 %, monocytes 6 %.

*Paul-Bunnell's test:* Positive (titer 2048).

16th day: *Liver biopsy.* The temperature now normal.

20th day: Jaundice diminished, fauces clear, the glandular swelling almost disappeared.

22nd day: Patient dismissed in good health.

WR —, Widal —, Weil —.

*Histological description of liver tissue.* (see fig. 1 and 2).

Very large specimen obtained by puncture; medium-size cells, approximately uniform in size with somewhat indistinct cell borders. The protoplasm is granular and vacuolized, but without fat content. The nuclei vary a little in size and in density of chromatin, but show no sign of biliary thrombi. Scattered mitoses. Here and there in the liver cells, but especially around the central vein there are considerable amounts of greenish pigment, and in the bile capillaries fine biliary thrombi. The portal areas show no definite increase in connective tissue, but large numbers of inflammatory cells, especially lymphocytes, plasma cells and numerous neutrophile and eosinophile leucocytes. The latter are also seen to extend a little out into the parenchyma. No bile duct proliferation and no sign of cirrhosis, tuberculosis or malignant tumor cell proliferation. The Kupffer cells are a little swelled and locally in mitotic division, but without any demonstrable pigment content. The glycogen content of the cells is natural.

*Microscopical diagnosis:* Hepatitis subacuta-subchron. inprimis interstit. periport. medio-magno grado.

Icterus levi grado.

*Comment:* Clinically, hematologically and serologically a well characterized case of infectious mononucleosis. Bile pigment in the urine a few days after the onset of the disease. Jaundice observed on the 7th day, liver biopsy on the 16th day shows moderate parenchymatous and severe portal, subacute inflammation as well as medium-severe jaundice and moderate proliferation and swelling of the Kupffer cells.

### *Case No. 3.*

29 years old lumberyard worker, hospitalized 20. 5—20. 6. 1944.

Sick 3 days before admission, with fever, headache, noncharacteristic abdominal pains and a few vomitings.

At the time of admission: Temperature 39° C. Mild tonsillitis, moderate enlargement of the cervical and inguinal glands, no enlargement of liver or spleen.

*Blood:* White blood count 11,700 per mm<sup>3</sup>. Differential count: Stab cells 7 %, polymorphonuclears 17 %, abnormal mononuclears (characteristic of mononucleosis) 55 %, ordinary lymphocytes 19 %, monocytes 2 %.

*Paul-Bunnell's test:* Positive (titer 256).

4th day of the disease: Mild jaundice of sclerae, bilirubin and urobilin in the urine. Icterus index (Meulengracht) 12.

5th day: Mildly icteric skin, icterus index 18.

6th day: *Liver biopsy.*

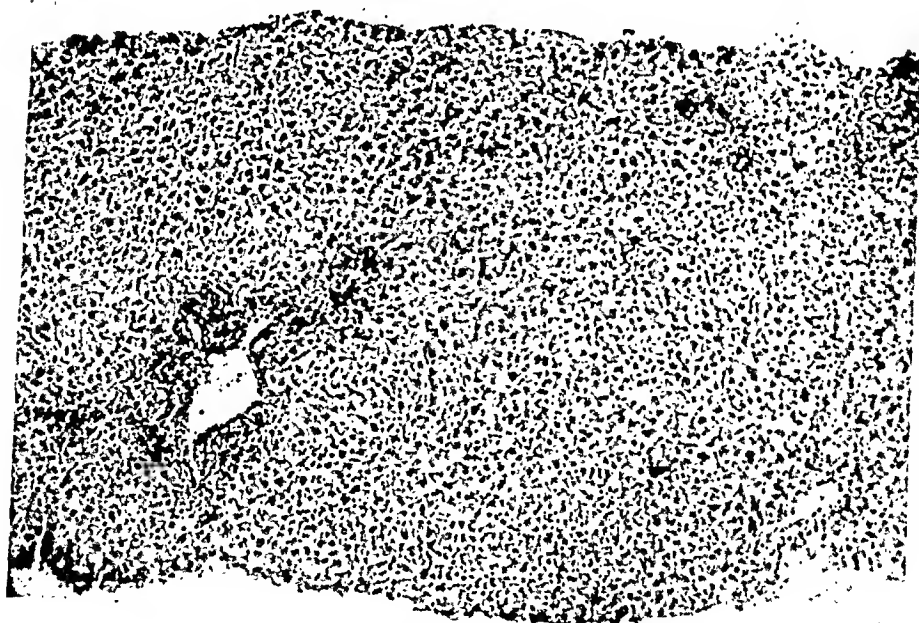
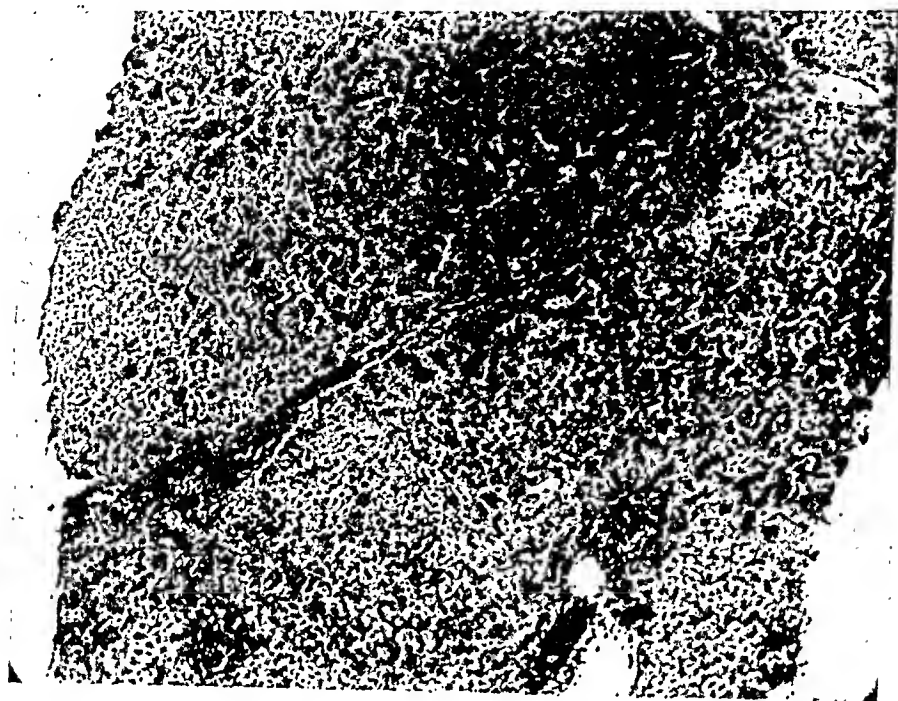


Fig. 1 and 2 (appr.  $\times 110$ )  
Interstitial inflammatory changes (see case No. 2).

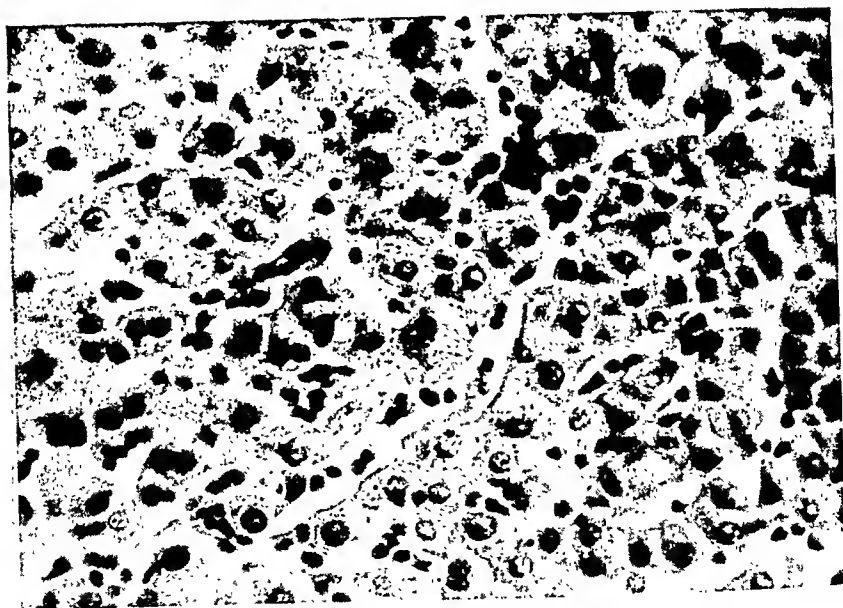
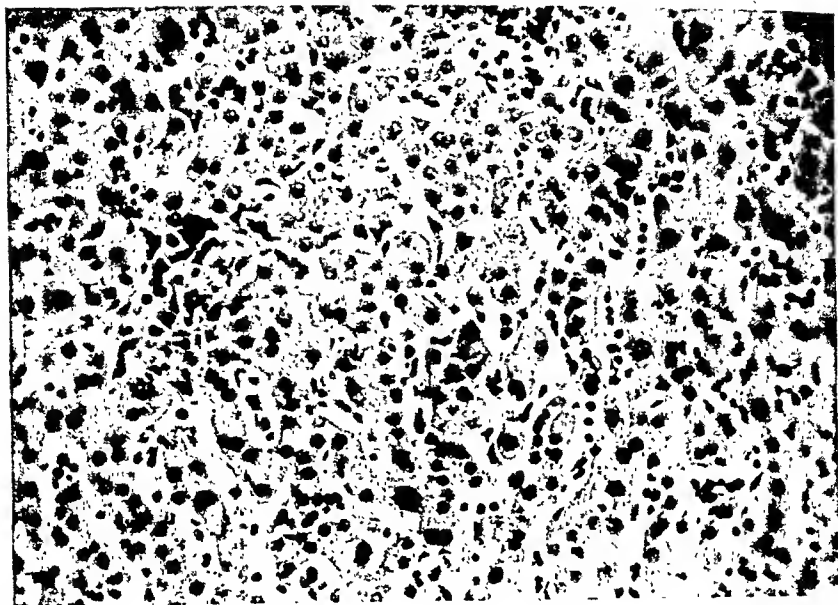


Fig. 3 and 4 (appr.  $\times 325$  and  $\times 400$ )  
Proliferation of reticulo-endothelial cells (see case No. 3).

The phenomena disappear in the course of about 10 days. Patient dismissed in good health on the 30th day.

*Histological description of liver tissue* (see fig. 3 and 4).

Large specimen obtained by puncture. The cells are of uneven size and with very vague cell borders. The protoplasm is granular and vacuolized. It is without fat content, here and there one observes a little greenish pigment; but no biliary thrombi. The nuclei vary in size and in chromatin density. There are scattered mitoses. Occasionally small vacuoles are observed in the nuclei and signs of beginning disintegration; in a few places only a ring-shaped shadow is seen in the place of nucleus. The connective tissue in the portal areas has not increased in amount here there is a considerable infiltration with lymphocytes and numerous neutrophile and eosinophile leucocytes, but only a very few plasma cells. The leucocyte infiltration extends a little out into the parenchyma. No bile duct proliferation. The Kupffer cells are here and there a little swelled and occasionally in mitotic division. In the sinusoids there are numerous detached, very small, mononuclear cells with sparse protoplasm and a little smaller than lymphocytes. The nuclei are round or slightly ovoid. A few of them are in mitotic division, and these appear to be in connection with the wall in the sinusoids, as distinct from the other nuclei which are detached. Presumably it is here a matter of proliferation of cells belonging to the reticulo-endothelial system. No sign of tuberculosis or malignant tumor cell proliferation. The carminestained preparation shows ample glycogen content.

*Microscopical diagnosis:* Hepatitis subacuta-subchron. inprimis interstit. periport. medio-magno grado.

Icterus levi grado.

*Comment:* Hematologically and serologically a well characterized case of infectious mononucleosis with jaundice from the 4th day. Liver biopsy on the 6th day shows medium-severe parenchymatous and portal, subacute infection as well as very mild jaundice and proliferation in the sinusoids of small lymphocyte-like cells, presumably originating from the reticulo-endothelial system.

#### Case No. 4.

36 years old seamstress, hospitalized 10. 7—11. 8. 1944.

Sick 9 days before admission, with fever and sore throat; the urine dark from the first day, the stools pale, but jaundice not noticed by those around the patient. Abdominal pain and vomiting after meals.

At the time of admission: Temperature 39.9° C. Jaundice of skin and sclerae, icterus index (Meulengracht) 36. Bile pigment and urobilin in the urine.

Tonsillitis with membrane formation, enlarged cervical, axillary and inguinal lymph glands. Enlargement of liver and spleen.

*Blood:* White blood count 31,000 per mm<sup>3</sup>. Differential count: Polymorphonuclears 28 %, eosinophile 2 %, abnormal mononuclears (characteristic of mononucleosis) 23 %, ordinary lymphocytes 28 %, monocytes 19 %.

*Paul-Bunnell's test*: Positive (titer 256).

17th day of the disease: *Liver biopsy*.

The temperature is normal after 3 weeks, the throat clear in the course of the 4th week, the jaundice and the glandular enlargement disappear shortly after.

32nd day: Patient dismissed in good health.

WR —, Widal —, Weil —.

*Histological description of liver tissue*.

Medium-size specimen obtained by puncture. The cells of medium-size, a little uneven in size, with nuclei of varying size and slightly varying chromatin density. No nuclear disintegration. A few mitoses of normal type. The cell borders are in most instances conspicuous, though here and there a little indistinct. The protoplasm is granular and slightly vacuolized, but without fat content. Insignificant amounts of greenish pigment are observed here and there, as well as a few, small, thin biliary thrombi in the bile capillaries. The interstitial connective tissue has not increased in amount, but in the portal areas there are moderate amounts of lymphocytes and plasma cells as well as neutrophile and eosinophile leucocytes. No inflammation in the parenchyma, and no bile duct proliferation. The Kupffer cells and the cells in the sinusoids as in case No. 3. No sign of tuberculosis or malignant tumor cell proliferation. The carmine-stained preparation shows ample glycogen content.

*Microscopical diagnosis*: Hepatitis subacuta-subchron. in primis interstit. periport, medio grado.

Icterus levi-medio grado.

*Comment*: Clinically, hematologically and serologically a typical case of infectious mononucleosis. Bile pigment in the urine already on the 1st day of the disease, jaundice observed on the 10th day. Liver biopsy on the 17th day shows medium-severe portal and mild parenchymatous, subacute inflammation, as well as mild-moderate jaundice and proliferation in the sinusoids of small cells, presumably originating from the reticulo-endothelial system.

## Discussion and conclusions.

The paper thus deals with 4 cases of mononucleosis complicated by jaundice. In all 4 cases the histological investigation of the liver tissue showed milder degenerative parenchymatous changes as well as medium-severe to severe interstitial inflammatory changes in the portal areas of subacute and milder subchronic nature (infiltration with round-cells and leucocytes). There is found interstitial increase of connective tissue and no necroses in the parenchyma. The jaundice demonstrated in the preparations has been mild in 2 cases and medium-severe in 2.

The changes have about the same appearance as in acute epi-

demic hepatitis, though with less pronounced parenchymatous and a little more severe interstitial changes.

The proliferation of »monocytoids» described by van Beek and Haex is presumably identical with the here described proliferation of small, lymphocyte-like cells in the sinusoids, and must undoubtedly be cells belonging to the reticulo-endothelial system. Whether this finding is characteristic of infectious mononucleosis is doubtful, since similar conditions may be found in biopsies of patients with other diseases. It is difficult, though, to form a clear picture of the changes in van Beek and Haex's case, since the histological description is very summary and brief.

The biopsy is carried out at somewhat different times in relation to the onset of the jaundice, but this has not demonstrably affected the histological picture, since the age of the process cannot with certainty be derived from this picture. The subacute character of the changes, even in the cases where the liver biopsy is carried out within a few days after the appearance of the jaundice, show, however, that the process has been going on for a certain length of time before manifesting itself in the icteric skin colour.

The histologically undoubted changes of degeneration and inflammation in connection with the relatively small amount of bile pigment in the cells, as well as the small biliary thrombi tell against a jaundice due to obstruction, and point instead to the presence of a primary damage to the liver which presumably is caused by the specific agent of the disease.

### Summary.

In 4 patients with infectious mononucleosis, complicated by jaundice, an investigation has been made of the histopathology of the liver with the aid of aspiration biopsy. Parenchymatous and interstitial inflammatory changes are observed, together with proliferation in the sinusoids of small, lymphocytelike cells, presumably belonging to the reticulo-endothelial system. No reason is found for considering obstruction the cause of the jaundice. It is here a question of a hepatitis which has set in early, or relatively early, in the disease, and which must be assumed to be attributable to the specific causative agent of this disease.



## References.

- Beek, C. van and A. J. Ch. Haex: *Acta med. scand.* 113, 125, 1943. — Buch, H.: cit. Thomsen, Stig. — Glanzmann, E.: *Das lymphämoide Drüsenfieber*. Berlin 1930. — Iversen, Poul and Kaj Roholm: *Acta med. scand.* 102, 1, 1939. — Mackey, R. D. and E. G. Wakefield: *Ann. Clin. Med.* 4, 727, 1926. — Nyfeldt, Aage: *Folia Hæmatolog.* 47, 1, 1932. — Roholm, Kaj and Poul Iversen: *Acta pathol. et microbiol. scand.* 16, 427, 1939. — Roholm, Kaj and Niels B. Krarup: *Ugeskr. f. Læg.* 103, 1163, 1941 & *Acta med. scand.* 108, 48, 1941. — Schwarz, E.: *Wien. Arch. f. inn. Med.* 19, 205, 1930. — Thomsen, Stig: *Studier over mononucleosis infectiosa*. (Dissert.) København 1942. — Øllgaard, E.: *Nord. Med.* 6, 671, 1940.
-

From the 3. Dep. of the Municipal Hospital of Copenhagen.

## Investigations on the Use of the Phycomyces Method in the Estimation of Vitamin B<sub>1</sub> in Blood.

By

H. O. BANG.

(Submitted for publication October 27, 1944).

---

Even though vitamin B<sub>1</sub> was the first of the vitamins to be discovered, and its discovery dates almost 50 years back, there are nevertheless a number of problems pertaining to this vitamin which are still in need of a solution. Among these problems is the one of the vitamin B<sub>1</sub> metabolism in the organism, including the presence of the vitamin in the blood — a problem which only in recent years has been made the subject of intensive investigations, and one which apparently is not yet completely solved. When our knowledge in this direction is still wanting it is first of all due to the lack of suitable, accurate and rapid methods for the estimation of vitamin B<sub>1</sub> in the body fluids, especially in the blood. The vitamin B<sub>1</sub> content of the blood is very small, about 0.10 microgram per ml, or 10,000 times smaller than, say, the glucose content, which explains the difficulties involved in an assay. It is different with the vitamin B<sub>1</sub> content of the urine; here the percentage is higher, and far larger amounts of liquid are available for an assay. Hence it is not surprising that serviceable methods have been developed for urine analysis, of which Jansen's thiochrome method, with its numerous modifications, deserves special mention.

When the question is that of a quantitative determination of such extremely small amounts of vitamin B<sub>1</sub> in the blood, one quite

naturally turns to biological methods. It is true that, in Germany the thiochrome method has been modified (Ritsert et. al.) for the purpose, thus a chemical method, but it is fairly well agreed that such methods hardly are capable of reflecting the almost infinitesimal variations in the vitamin B<sub>1</sub> content of the blood which must be recorded. Among the biological methods it is especially the so-called *Phycomyces* method which attracts attention at present, and this paper is devoted to a study of what may be expected from this method. One other method may be mentioned here as rather promising, viz., the cocarboxylase activation method, proposed by Ochoa and Peters (1938) and further developed and modified by Westenbrinck, Parvé, van der Linden and van den Broek (1943); it is now reported to be very accurate and specific. The method determines only the phosphoric ester cocarboxylase of the vitamin B<sub>1</sub> in the blood i.e., the biologically active form of the vitamin. The *Phycomyces* method determines the sum of cocarboxylase and the free vitamin B<sub>1</sub> in the blood.

The following deals with the important questions pertaining to the applicability of such a biological method, viz., 1) specificity for known growth promoting substances, 2) possible susceptibility to the effect of other substances in the blood besides vitamin B<sub>1</sub>, 3) accuracy.

We shall first describe, briefly, the technique employed; it is in all essentials that proposed by Meiklejohn (1937), later slightly modified by Lehmann and Nielsen (1941); reference is made to these authors as regards details. The fungus *Phycomyces Blakesleeanus* grows but very poorly on a medium composed of glucose 10 %, primary potassium phosphate 0.15 %, magnesium sulphate 0.05 %, and 1-asparagine 0.2 or 0.4 % — but if vitamin B<sub>1</sub>, or a substance containing this vitamin is added, the fungus begins to grow, and the magnitude of the growth is a direct measure of the vitamin B<sub>1</sub> added. The fungus is collected after 10 days of growth, rinsed, dried and then weighed. A standard growth curve is plotted on the basis of the growth in a series of flasks to which increasing amounts of vitamin B<sub>1</sub> have been added, e.g., from 0 to 0.20 microgram per 1 cm<sup>3</sup>. Knowing the weight of the fungus from a flask containing, say, 1 cm<sup>3</sup> of blood, it is possible by interpolation on this standard curve to find an expression for the vitamin B<sub>1</sub> content of the blood.

The course of the standard curve shows at first a steep ascent, then it is deflected more and more, finally running parallel to the axis of abscissa; further addition of vitamin B<sub>1</sub> causes no additional growth (fig. 1). Various reasons make it desirable to work with a rectilinear curve. The standard growth curve may be transformed into such curve — at least in so far as its lower part is concerned — by logarithmic plotting of ordinates and abscissae.

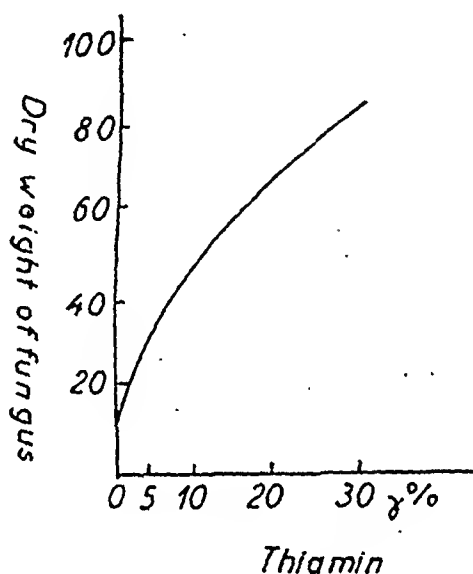


Fig. 1. Standard growth curve.

This procedure is followed here, especially since it is the lower part of the curve that is of most practical use, representing as it does vitamin B<sub>1</sub> additions of less than 0.20 microgram per cm<sup>3</sup>. The standard growth curve intersects the axis of ordinates a little above the O-point, indicating that flasks without vitamin B<sub>1</sub> addition show a certain, slight fungus growth (as a rule 8—12 mg) owing to the contents of growth promoting substance in the spores added; the author has shown that these spores contain about  $2 \times 10^{-8}$  microgram each. The nature of this growth substance is unknown, but it is natural to regard it as vitamin B<sub>1</sub>. In order to plot the vitamin B<sub>1</sub> content of the flasks as abscissae, it is necessary to know the value of the amount of vitamin added with the spores. An adequate measure of this amount may be obtained as follows:

The standard growth curve is — in its lower part — approximately parabolic. When the ordinate values of a parabola are squared, the curve becomes a straight line. The rectilinear extension of the standard growth curve to the left of the axis of ordinates intersects the axis of abscissa a little to the left of its O-point (see fig. 2). It will be seen that the distance from this O-point to the intersection between the extension of the rectilinear standard curves

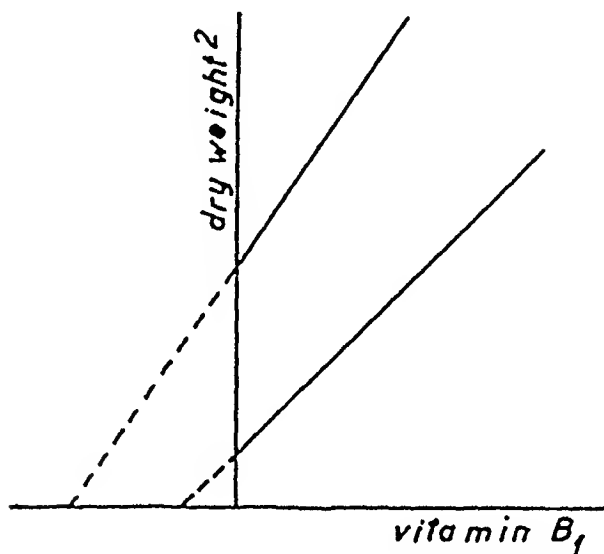


Fig. 2. Standard (below) and blood growth curves.

and the axis of abscissa represents the vitamin B<sub>1</sub> content of the flasks to which no extraneous vitamin B<sub>1</sub> has been added, *i.e.*, the vitamin B<sub>1</sub> from the spores. If this quantity is thus defined, it may be added to the vitamin B<sub>1</sub> additions to the standard flasks, whereupon the plotting is done logarithmically. Then we interpolate with the logarithm of the dry weight in a flask containing blood, on the logarithmic curve, thus obtaining the logarithm of the vitamin B<sub>1</sub> content of the sample, whereupon the antilogarithm is found.

Using the method of least squares it is possible also to *calculate* the vitamin B<sub>1</sub> content of a sample, the procedure being as follows: The value, B<sub>0</sub>, of the vitamin B<sub>1</sub> content of the spores is deter-

mined. A determination is then made of the vitamin  $B_1$  values of the standard series (*i. e.*, added vitamin  $B_1 + B_0$ ) ( $x$ ), and of the mean of the dry weights ( $y$ ) corresponding to the individual vitamin  $B_1$  additions obtained from double experiments. The middle point ( $\bar{x}$ ,  $\bar{y}$ ) on the rectilinear regression line  $y - \bar{y} = b(x - \bar{x})$  (see fig. 3) corresponding to the logarithmic values is calculated according to the formulae

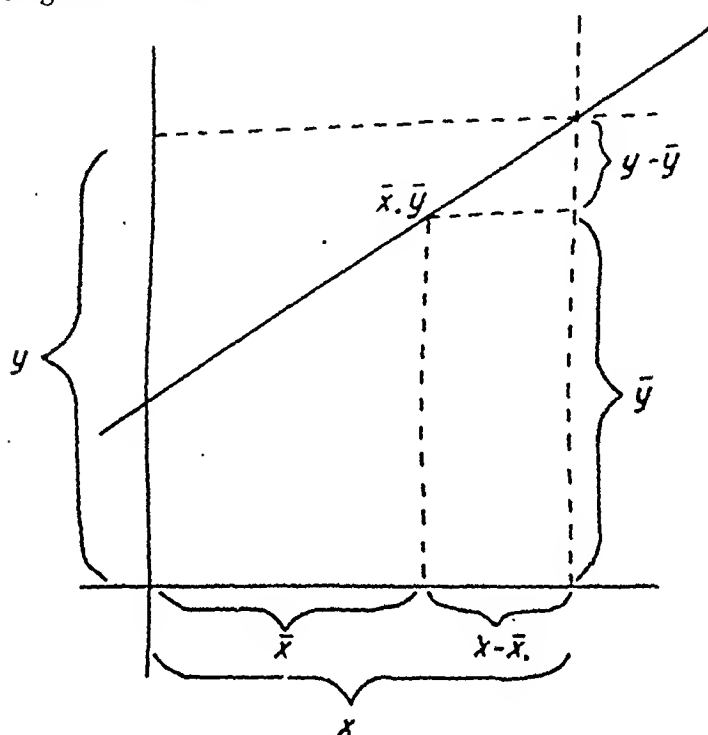


Fig. 3. The regression line for a standard curve.

$$\bar{x} = \frac{\sum S_x}{\sum n} \quad \bar{y} = \frac{\sum S_y}{\sum n}$$

where  $S_x = x \cdot$  the number of determinations of this dose,  $S_y =$  the sum of the  $y$ 's of the individual doses, and  $n =$  the number of observations.

$b$ , which is the slope of the rectilinear regression line, is calculated from

$$b = \frac{SP_{xy}}{SK_x}$$

where  $SK_x$  (the sum of squares of  $x$ ) is calculated from

$$SK_x = \frac{\sum S_x^2}{n} \div \frac{(\sum S_x)^2}{\sum n}$$

and  $SP_{xy}$  (the sum of the products of  $x$  and  $y$ ) from

$$SP_{xy} = \sum \frac{S_x S_y}{n} \div \frac{\sum S_x \cdot \sum S_y}{\sum n}$$

When the rectilinear regression line corresponding to the standard curve is determined, it is now possible, knowing the logarithm of the growth in a flask with blood, to locate the logarithm of the corresponding vitamin  $B_1$  dose, or the logarithm of the dry weight in the flask with blood is inserted in the formula

$$\log \text{ Vitamin } B_1 = \frac{y \div \bar{y}}{b} + \bar{x}$$

thus giving the value of  $\log$  vitamin  $B_1$ .

## 1. Specificity.

The starting point for Schopfer's discovery of the vitamin  $B_1$  as a necessary growth-promoting factor for *Phycomyces* is to be found in the observation that this fungus on a medium prepared from malt extract, yeast extract, bread, or the like, showed natural development, with the formation of sporangia. On a synthetic medium (modified Coon's substrate) the fungus showed but slight development, and no sporangia appeared. The addition of a certain maltose preparation (Kahlbaum) gave full growth, however. Alcoholic extracts of the maltose proved it to contain the active substance, and various physical and chemical properties of the unknown growth substance indicated that it belonged to the vitamin B complex. Experiments with the growth substance and crystalline vitamin  $B_1$  showed no difference whatever between the two substances.

Schopfer has moreover investigated the effect of a number of other growth-promoting substances on *Phycomyces*, and reviews the results in a paper from 1939. The substances are partly other vitamins, especially of the B-complex (nicotinic acid, riboflavin.

and adermin), but also ascorbic acid, and partly the so-called bios as well as a few other substances which were known to promote the growth of different microorganisms (especially bacteria); as examples may be mentioned hematin, cholesterol, pimelic acid, and cozymase. None of these substances must of necessity be furnished Phycomyces from without in order to give the fungus normal growth, but that does not mean that none of them are growth promoting substances for Phycomyces. Thus it is found that Phycomyces mycelium contains ample amounts of bios, active for yeast fungi [Schopfer (1935)]. These bios must be assumed to be a necessity to Phycomyces, but can be synthesized by the fungus itself. According to Wassink (1934) the growth of Phycomyces is not affected by auxin, nor does heteroauxin have any effect [Schopfer (1935)].

Meiklejohn (1937) has also investigated different substances with a view to determine the possible effect on the growth of Phycomyces. A bios preparation with strong growth promoting activity for yeast had no effect on Phycomyces. The same preparation was later tested by Sinclair (1938) however, who found it to have a very pronounced effect. It is difficult to explain this discrepancy. Meiklejohn also investigated mannitol which, according to Reader (1929), acts as an aid factor in the vitamin B<sub>1</sub>'s stimulation of a *Streptothrix*, and found the substance to have no effect on the growth of Phycomyces. A preparation possessing growth-promoting properties for staphylococci (Knight) had only negligible activity for Phycomyces. That the substance nevertheless had some effect is undoubtedly due to the circumstance that, according to Knight (1937), it consists to some extent of degradation products of vitamin B<sub>1</sub>.

Kögl and Fries (1937) found biotin (isolated as methyl ester from egg yellow) to have no effect on the growth of Phycomyces.

Sinclair (1938) found that «coenzyme I and II», riboflavin and  $\beta$ -alanine were without effect on Phycomyces. A preparation of vitamin B<sub>6</sub> (adermin) was without effect when alone, but acted as growth promoting substance when together with thiamin.

The present author has investigated various substances known to stimulate the growth of different microorganisms, in order to determine whether they had any influence on the growth of Phycomyces. The investigation included nicotinic acid amide, riboflavin and adermin (vitamin B<sub>6</sub>). Amounts of 0.5 microgram were



Table 1.

Investigation on the possible effect of different growth-promoting substances on the growth of *Phyeomyces* (double experiments)

Vitamin B <sub>1</sub> microgram	Blood cm <sup>3</sup>	Nicotinic acid amide microgram	Riboflavin microgram	Adernin (B <sub>6</sub> ) microgram	Biotin microgram	$\beta$ -alanine microgram	Pantothenic acid micro- gram	p-amino benzoic acid microgram	Inositol microgram	Growth mg
—	—	—	—	—	—	—	—	—	—	11 9 9 9.5
—	—	0.5	—	—	—	—	—	—	—	8 9
—	—	—	0.5	—	—	—	—	—	—	8 9
—	—	—	—	0.5	—	—	—	—	—	9 9
—	—	—	—	—	0.02	—	—	—	—	19 23
—	—	—	—	—	0.02	10	10	2.5	100	20.5 22
0.20	—	—	—	—	—	—	—	—	—	69 74
0.20	—	0.5	—	—	—	—	—	—	—	72 74
0.20	—	—	0.5	—	—	—	—	—	—	74 69
0.20	—	—	—	0.5	—	—	—	—	—	70.5 73
0.20	—	—	—	—	0.02	—	—	—	—	72 74
0.20	—	—	—	—	0.20	10	10	2.5	100	72 76
—	1	—	—	—	—	—	—	—	—	51 55
—	1	0.5	—	—	—	—	—	—	—	48 44.5
—	1	—	0.5	—	—	—	—	—	—	54 —
—	1	—	—	0.5	—	—	—	—	—	46.5 46
—	1	—	—	—	0.02	—	—	—	—	50 55
—	1	—	—	—	0.02	10	10	2.5	100	50 52

added to flasks prepared in the usual manner. Other substances included were biotin,  $\beta$ -alanine, pantothenic acid, p-amino benzoic acid, and inositol, which in the form of a mixture were added in amounts of 0.02—10—10—2.5 and 100 micrograms per flask. Finally, flasks were prepared containing biotin alone in an amount of 0.02 microgram. In order to investigate whether the above mentioned substances had any influence on the growth-promotion produced by vitamin B<sub>1</sub> or by blood, flasks were prepared with the growth-promoting substances added in the above amounts 0.2 microgram of vitamin B<sub>1</sub> or 1 cm<sup>3</sup> of blood per flask. The results of these experiments are given in table 1.

The table shows that with the exception of biotin none of the substances mentioned affected the growth of *Phycomyces*, either when they were present alone in the concentrations given, or when the addition also included 0.2 microgram of vitamin B<sub>1</sub> or 1 cm<sup>3</sup> of blood; in the last mentioned instance there was perhaps a slight inhibition of the growth in the flasks with nicotinic acid amide and adermin. In the flasks containing biotin or a mixture of biotin with  $\beta$ -alanine, pantothenic acid, p-amino benzoic acid and inositol, a certain small growth was observed when no vitamin B<sub>1</sub> or blood was present, the growth being equivalent to that produced by an addition of 0.0175 microgram of vitamin B<sub>1</sub> estimated by means of a standard growth curve found in the same experiment. Biotin and mixtures of biotin and the other growthpromoting substances mentioned gave rise to the same stimulation of growth, from which it is concluded that this stimulation is due to the biotin alone. If, however, there was observed a reasonably strong growth owing to the addition of blood or 0.2 microgram of vitamin B<sub>1</sub> (this addition in no way giving maximal growth of *Phycomyces*), then the biotin addition did not cause any stimulation of the growth.

Since biotin was the only one of the substances investigated which affected the growth of *Phycomyces*, it was deemed advisable to investigate the behaviour of this substance a little further. Hence an experiment was carried out in which increasing amounts of biotin (from 0 to 0.32 microgram) were added to a series of flasks containing ordinary medium (0.4 % asparagine). The details of the experiment are recorded in table 2 and fig. 4.

Table 2 and fig. 4 — the latter also including a thiamin growth curve from the same experiment — show that the biotin, just like

Table 2.

The growth of *Phycomyces* after the addition of different amounts of biotin (double experiments).

Biotin in microgram per 10 cm <sup>3</sup> of medium	Dry weight of <i>Phycomyces</i>		
	Double experiment		Mean
0	7	7	7
0.02	23	23	23
0.04	27	40.5	33.75
0.08	53	55.5	54.25
0.16	68	65	66.5
0.32	61	70	65.5

the vitamin B<sub>1</sub>, stimulates the growth of *Phycomyces*, and that the growth attained with equal weights of the two substances is approximately the same. Like the vitamin B<sub>1</sub> growth curve, the biotin growth curve follows at first a steeply ascending course, whereupon the additional growth obtained by further amounts of biotin becomes steadily less, until an optimum is reached for the addition of biotin beyond which no additional growth is produced. The biotin used, which was prepared at the Fermentation-Physiological Department of the Carlsberg Laboratory and furnished through the courtesy of the Director, Dr. Niels Nielsen, must be considered very pure without being chemically pure. Repeated recrystallizations of the extremely valuable substance would be required to make the purity absolute, and the amount available was insufficient for the purpose. Whatever impurities may have been present, the shape of the curve obtained shows that the biotin preparation cannot have contained any significant contamination of vitamin B<sub>1</sub>.

Since biotin is very commonly found in nature, one might quite naturally think that it might be present in blood to such an extent as to affect the growth of *Phycomyces* and thus give rise to errors in the method. As far as the author is aware, only one paper has been published dealing with the biotin content of blood, *viz.*, by Nielsen and Hartelius (1942). The paper describes a method for the determination of biotin in organic fluids, *e. g.*, in ox serum and pig's serum, where it reports a biotin content of 4.3 and 6.5 one-thousandth of a microgram per cm<sup>3</sup> for the former and 6.5 and 6.5

one-thousandth of a microgram for the latter. No data are available on the biotin content of human blood. Assuming, however, that human serum contains about the same amount of biotin as the two sera mentioned, and that the formed elements of the blood do not contain noticeable amounts of biotin, it follows that the biotin content of human blood is about 10 times less than its thiamin con-

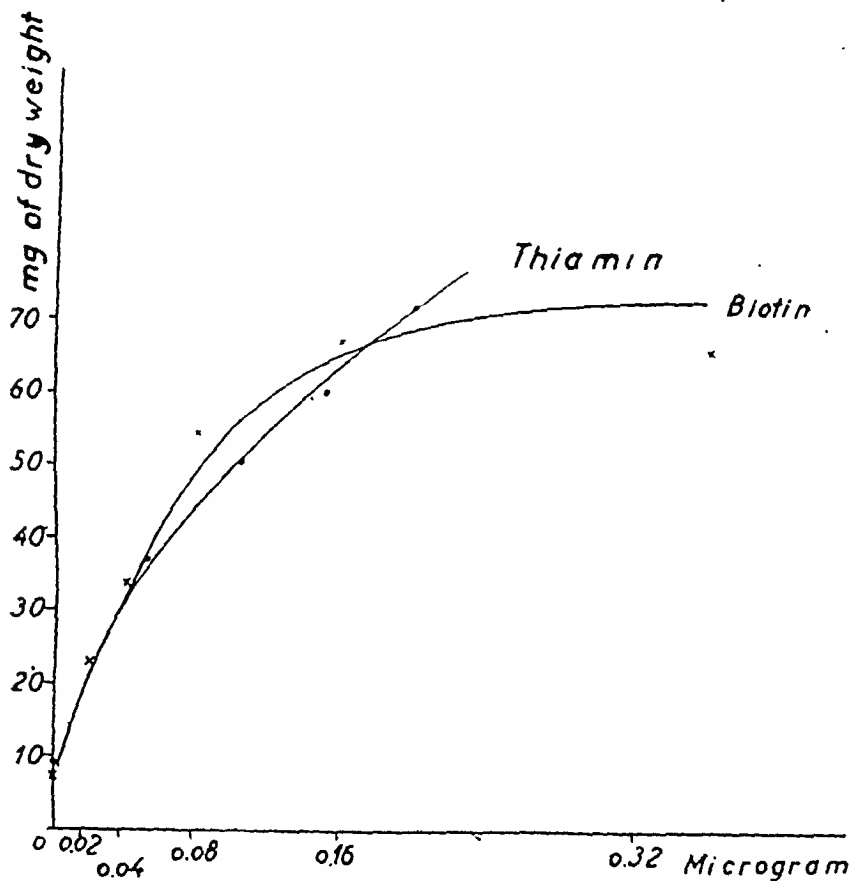


Fig. 4. Biotin and thiamin growth curves for *Phycomyces*.

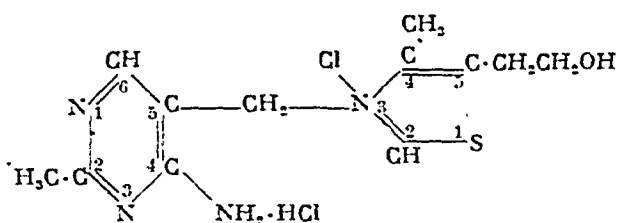
tent. Since biotin and thiamin stimulate the growth of *Phycomyces* to about the same degree, it is seen that the error of the *Phycomyces* method attributable to biotin in the blood at the most amounts to 10 %. But it is seen from the results in table 1 that the error probably is far less, the table showing, as previously mentioned, that the biotin action due to an amount of biotin so relatively large as 0.02 microgram is completely masked when vitamin B<sub>1</sub> (here 0.20 microgram) or 1 cm<sup>3</sup> of blood is added. In fact,

instead of acting as a kind of »thiamin catalyst», or, as Sinclair would say, an »adjuvant factor», for the vitamin B<sub>1</sub>, the biotin action does not appear at all when vitamin B<sub>1</sub> is present, regardless of whether it is added as such or present in the added blood.

Considering what has been said here it seems justified to say that vitamin B<sub>1</sub> is a growth promoting substance, specific for *Phycomyces*, and that it has not been proved that the growth of *Phycomyces* is affected by any of the generally known substances which are recognized as growth-promoting for a series of other microorganisms or fungi. Biotin is an exception to the rule; it stimulates the growth of *Phycomyces* approximately to the same extent as thiamin, but its action is masked by the presence of thiamin or thiamin-containing blood.

A series of investigations have shown, however, that the specificity of thiamin for *Phycomyces* is not absolute, since there exists a number of substitution products of thiamin which more or less stimulate the growth.

The structural formula of thiamin is



(Thiamin chloride hydrochloride).

In the animal the constitutional specificity is apparently very pronounced. According to Peters and O'Brien (1938) substitution products of the thiamin molecule in which the hydroxyethyl group of the thiazole is replaced by a hydrogen atom, a hydroxypropyl group, or an ethyl chloride group — the methyl group of the pyrimidine by a chlorine atom — or where combinations of such substitutions occur — are completely or almost completely inactive in the case of rats. If the methyl group of the pyrimidine is replaced by an ethyl group, or is moved from the 2-position to the 6-position, the substance shows only 50 % of the normal thiamin action.

In the vegetable kingdom, and here especially in the case of *Phycomyces*, the constitutional specificity is a little less pronounced. Of the substitution products with starting point in the

thiamin molecule Schopfer (1939) finds ethyl thiamin (a methyl group exchanged with an ethyl group in the 2-position of the pyrimidine) the only one to be as active as the thiamin. (In passing it may be recalled that the pyrophosphoric ester of thiamin, cocarboxylase, is as active for *Phycomyces* as the thiamine itself).

As previously mentioned, *Phycomyces* belongs to the organisms whose growth is stimulated just as well by a mixture of the components of thiamin — pyrimidine and thiazole — as by the thiamin itself. A few of the substitution products of these two units are also active. Thus in the 5-position of the thiazole the group  $\text{CH}_2\text{CH}_2\text{OH}$  may be replaced by  $\text{CH}_2\text{CH}_2\text{Cl}$  or by  $\text{CH}_2\text{CH}_2\text{OCOC}_2\text{H}_5$  [Robbins and Kavanagh (1938 II)]. Also 3-benzyl-4-methyl-5- $\beta$ -hydroxyethyl thiazole and 3-(4'(5'))-methyl-imidazole-4-methyl-5- $\beta$ -hydroxyethyl thiazole are active [Schopfer (1937 II)]. In the 5-position of the pyrimidine the  $\text{CH}_2\text{NH}_2$ -group may be replaced by a few other groups, *e.g.*,  $\text{CH}_2\text{NHCHS}$  [Robbins and Kavanagh (1938 I)], eventually with a simultaneous exchange of the methyl group in the 2-position with an ethyl group [Schopfer (1939)]; it may likewise be exchanged with a  $\text{CH}_2\text{Br}$ -group [Robbins and Kavanagh (1938 I)].

On the whole, however, it seems that the constitutional specificity for *Phycomyces* is very pronounced. It is only a few atom groups which are unimportant for this organism, and it is only within rather narrow limits that substitutions in these two groups yield active substances.

According to Schopfer, an investigation of the effectivity of a substitution product for an organism should involve the use of a concentration of the substance which is equimolar with the optimal concentration of the original substance (thiamin, pyrimidine or thiazole), since it is found that otherwise inactive substitution products are active when present in higher concentrations.

Lehmann and Nielsen (1941) regard the question of the specificity of the fungus method as not fully answered. They consider it most correct to designate the amounts of vitamin  $\text{B}_1$  found by this method as »vitamin  $\text{B}_1$  equivalents». However, they have determined the vitamin  $\text{B}_1$  content of a yeast preparation standardized by the rat-bradycardia method and found complete agreement between the two methods.

## 2. Substances in the blood other than vitamin B<sub>1</sub> which affect the growth of *Phycomyces*.

Schopfer and Jung (1937) were the first who tried to estimate the vitamin B<sub>1</sub> content of blood by means of the *Phycomyces* method. They warned against the use of the method in the case of urine, finding that the urine contained substances which affected the fungus growth without being vitamin B<sub>1</sub>. Meiklejohn, who further developed the method for the use in blood analyses (1937) states that it is specific, i.e., that vitamin B<sub>1</sub> is alone, also in the case of blood, in affecting the growth of the *Phycomyces*; known amounts of vitamin B<sub>1</sub> added to the blood can be demonstrated quantitatively in the assay, and there is agreement between values found upon the addition of 1 and 2 ml of blood. Meiklejohn must have been aware, however, that an addition of blood to the medium for the fungus affects the growth since he proposes to use an asparagine content of 0.4 % in the flasks of the standard series, but finds the results most satisfactory with 0.2 % of asparagine when blood is present. He has investigated the significance of the asparagine concentration of the medium and found that the growth of the fungus with high vitamin B<sub>1</sub> addition is inhibited or even ceases when the asparagine content of the medium is too small. He finds an asparagine concentration of about 0.4 % optimal, i.e., a further increase of the concentration does not produce further growth, even for an excess of vitamin B<sub>1</sub>. The present author, however, has conducted experiments which show that the optimal asparagine concentration is as high as 0.7 % in the presence of an excess of vitamin B<sub>1</sub>.

A paper by Sinclair (1938) subjects these questions to a critical examination. Sinclair disputes the claim that vitamin B<sub>1</sub> added to the blood can be determined quantitatively in the assay; as a rule he finds a growth of the fungus greater than that corresponding to the spontaneous vitamin B<sub>1</sub> content of the blood + the vitamin B<sub>1</sub> added, and he speaks of the «adjuvant factor» of the blood which he attributes partly to the buffer action of the blood and partly to unknown substances in the blood. In a later paper (1939) he proposes a method for correcting this error — a method which it is necessary to consider at this time since it has found its place in later vitamin B<sub>1</sub> literature [Westenbrinck et al. (1943)] and there

is regarded as so correct that, according to the authors cited, one may ignore all results obtained by the *Phycomyces* method when Sinclair's correction has not been applied. The basis for Sinclair's correction is erroneous, however, as will be shown in the following.

In his paper from 1939 Sinclair introduces a method which should furnish a correction for the effect on the growth which is caused by the blood, but is not due to the vitamin  $B_1$  in the blood. His starting point is the above mentioned fact that the addition of blood to flasks with an excess of vitamin  $B_1$  produces a far stronger fungus growth than that obtainable in flasks with vitamin  $B_1$  in excess but with no blood. Moreover, that the addition of small, known amounts of vitamin  $B_1$  to blood frequently produces a fungus growth that is somewhat greater than one would expect from the original vitamin  $B_1$  content of the blood. Sinclair now assumes that the growth caused by a given amount of vitamin  $B_1$  in the presence of blood, in the case of each separate sample of blood, is in a definite ratio to the growth produced by the same amount of vitamin  $B_1$  in the absence of blood, and he proposes to correct for the adjuvant factor of the blood by multiplying the dry weight of the fungi which have grown in the flasks by the factor

Weight of fungus obtained with excess vitamin  $B_1$

Weight of fungus obtained with excess vitamin  $B_1$  + blood

Oh course, he is dealing with the same blood. Since, as mentioned, the growth in the flasks with blood and excess of vitamin  $B_1$  as a rule is greater than the growth in the flasks with excess of vitamin  $B_1$  alone, the above factor is less than 1, and the corrected weight of fungus less than the uncorrected weight. Using the reduced fungus weight Sinclair now interpolates on a standard growth curve obtained in the same experiment. He states that this method of correction gives conformable values, regardless of whether 1, 2 or 3 ml of blood are used, and permits the quantitative determination of the amounts of vitamin  $B_1$  added to the blood. — Sinclair states that the crucial test of this method of correction would be to add known amounts of vitamin  $B_1$  to blood from which the vitamin has been removed, but it has as yet been impossible to remove or destroy the vitamin  $B_1$  in the blood without affecting the adjuvant factor.



Sinclair's method of correction, in its present form, is not accurate however, since it does not pay any attention to the nitrogen content of the medium — a point which oddly enough, he had much to say about in his first paper. It was shown already by Meiklejohn (1937) that the nitrogen content of the medium is of great importance to the growth of the fungus, especially when large amounts of vitamin B<sub>1</sub> are added. Meiklejohn uses asparagine as nitrogen source. He finds that an asparagine content of 0.2 % gives less growth than a concentration of 0.4 % when an excess of vitamin B<sub>1</sub> is added. In other words, that the nitrogen of the medium acts as a growth-limiting factor when present in concentrations too small in proportion to the amount of vitamin B<sub>1</sub> added. For various reasons Meiklejohn uses 0.4 % of asparagine in the flasks without blood, but 0.2 % in the flasks with blood. Sinclair (1938) is of the opinion, however, that 0.4 % of asparagine is the optimal concentration in all flasks.

In his own experiments on the influence of the asparagine concentration on the fungus growth, the present author finds that the optimal concentration is as high as 0.7 %, so that the growth in flasks with 0.4 % of asparagine and excess of vitamin B<sub>1</sub> ceases because the nitrogen supply is insufficient (table 3).

In the main, the technique was that described by Meiklejohn. In addition to asparagine the medium contained 10 % dextrose, 0.05 % MgSO<sub>4</sub> and 0.15 % KH<sub>2</sub>PO<sub>4</sub>. 50 ml Erlenmeyer flasks were used, containing 10 ml of medium. Sterilization at about 110° C for 10 minutes. Inoculation with a suspension of about 1 million spores per ml. Time of growth 10 days. Drying of the rinsed fungus to constant weight. Weighing.

In Sinclair's correction the growth produced by excess of vitamin B<sub>1</sub> is used where, as shown, the growth ceases because of insufficient available nitrogen in the flasks without blood. However, blood is a highly nitrogenous fluid, which means that in the flasks with blood (and excess vitamin B<sub>1</sub>) there should be a possibility of growth beyond that in flasks without blood (asparagine content of the medium 0.4 %) if the fungus is capable of utilizing the nitrogenous compounds originating from the blood. The sterilization of the flasks will, however, cause a coagulation of some of the nitrogenous compounds of the blood, so that possibly they are no longer

Table 3.

The effect of different asparagine concentrations on the growth of *Phycomyces* (Double experiments).

Vitamin B <sub>1</sub> added microgram	Asparagine concentration 0.2 % mg dry weight	Asparagine concentration 0.4 % mg dry weight	Asparagine concentration 0.7 % mg dry weight	Asparagine concentration 1.0 % mg dry weight
0	12.5	7	11	16
	18	9	11	19
		12		17.5
0.01	19	16	24.5	25
	17	16	21	30.5
0.025	27	30	29	34
	28.5	29	29	33
0.10	43	46	51.5	53
	42	50	51	56
0.25	57	77	82	82
	56	79.5	82	77
1.00	70	114.5	160	142
	71	114.5	160	160

available for the *Phycomyces*. In order to investigate this question, the following experiments and calculations were made.

The nitrogen content of the medium before and after the addition of blood and sterilization may be estimated on the basis of the asparagine concentration of the medium and determined by analysis [a micro-Kjeldahl method was used, described by Peters and van Slyke (1932)]. Table 4 shows that the amount of dissolved, nitrogenous compounds in the medium increases very materially due to the addition of blood — *e.g.*, by about 50 % when the asparagine concentration is 0.4 %.

The nitrogen which in the presence of blood is found in the medium in solution is not the only nitrogen, however, which is at the disposal of the fungus. The fact is, that a nitrogen analysis on the medium after completion of growth (10 days) and after removal of the fungus shows that in certain cases the medium at this time contains more dissolved nitrogen than one would expect on the basis of the nitrogen present at the beginning of the growth and that consumed in the building up of the fungus. Kjeldahl analyses of the dried fungus have shown that the nitrogen content is 5.6—

Table 4.

Determination of nitrogen content of medium without blood and of medium with blood, after filtering off the heat-coagulating proteins (double experiments and mean values).

	Asparagine concentration 0.2 %		Asparagine concentration 0.4 %		Asparagine concentration 0.7 %	
Calculated N in mg per 10 ml .....	3.7		7.5		13.1	
N found in mg per 10 ml .....	3.4	3.1	7.3	7.1	13.5	12.8
	2.8		6.9		12.1	
N found in mg per 10 ml after addition of 1 ml oxalated blood and filtering off the protein coagula	6.2	6.2	11.5	11.0	15.9	15.7
	6.3		10.4		15.4	
N originating from added blood, in mg per 10 ml	3.1		3.9		2.9	

6.2 %, average 5.83 %. On the basis of this figure and our knowledge of the nitrogen content of the medium it is possible to estimate the maximal fungus growth attainable.

Table 5 shows that the fungus in the flasks with asparagine concentration 0.2 % has not only used, for its growth, the nitrogen that was available in the form of dissolved nitrogenous compounds, originating partly from the asparagine and partly from the nitrogenous constituents of the blood that were not coagulated by heating, but that, in order to attain its strong growth it has had to use some of the nitrogen that was found in the protein coagula, which it therefore must have been capable of splitting by means of a proteolytic enzyme. — Conditions are a little different in the flasks with 0.4 % of asparagine; here it has not been necessary for the fungus to split undissolved nitrogen from the coagula to attain its growth, since it has been able to get along with the asparagine nitrogen plus that originating from the dissolved nitrogenous constituents of the blood (after sterilization).

Following these observations regarding the nitrogen exchange of the *Phycomyces* we shall return to Sinclair's correction. The starting point was that the growth caused by a given amount of vita-

Table 5.

Determination of the nitrogen content of the filtered medium after addition of blood, before and after the growth. (Double experiments and mean values.)

	Asparagine concentration 0.2 %		Asparagine concentration 0.4 %	
N found before the beginning of growth, in mg per 10 ml .....	6.2 6.3	6.2	11.5 10.4	11.0
Dry weight of fungus after 10 days growth with excess of vitamin B <sub>1</sub> , in mg .....	125 140	132	138 147	143
N consumed for the growth of the fungus, in mg .....	7.7		8.4	
N found in filtered medium after 10 days growth, in mg per 10 ml.....	2.7		2.2	
Estimated N residue in medium after 10 days growth, in mg per 10 ml .....	-1.5 (6.2-7.7)		2.6 (11.0-8.4)	

min B<sub>1</sub> (i.e., also by an excess of vitamin) in the presence of blood is in a fixed ratio to the growth produced by the same amount of vitamin B<sub>1</sub> in the absence of blood. This is perhaps true, but in that case only for amounts of vitamin B<sub>1</sub> below the optimum. With the optimal amount, or with an excess of vitamin B<sub>1</sub> (and it is this addition of vitamin that Sinclair uses to get around the effect of the vitamin spontaneously present in the blood) the growth ceases in the flasks without blood, because the nitrogen source is exhausted, while the growth in the flasks with blood, where the nitrogen supply from the blood is an unknown quantity, at any rate does not stop for lack of nitrogen.

Thus it will be seen that the theoretical foundation for Sinclair's correction is inadequate.

The present author has previously [Bang (1942)] described a method of correction in which it is endeavoured to find the actual vitamin B<sub>1</sub> content of the blood. The method makes use of the above mentioned fact that a parabola is transformed into a straight line when its ordinate values are squared. Both the standard growth curve as well as the curve representing the growth in flasks containing blood without and with known, increasing amounts of vitamin B<sub>1</sub> (the «blood growth curves») follow a reasonably parabolic course,

at any rate as far as their lower part is concerned, *i.e.*, for vitamin B<sub>1</sub> contents of the flasks  $\cong$  0.20 microgram. Drawn with squared ordinate values, the curves assume the appearance shown in fig. 2.

The vitamin B<sub>1</sub> content of a flask containing a blood sample to which no vitamin B<sub>1</sub> has been added is seen to be equal to the distance from the 0-point of the axis of abscissa to the point of intersection between the rectilinear extension of the «blood growth curve» to the left of the axis of ordinates and the axis of abscissa. To get the vitamin B<sub>1</sub> content of the blood sample itself, it is necessary to deduct the value of the vitamin B<sub>1</sub> content of the spores, which corresponds to the distance from the 0-point to the point of intersection between the rectilinear extension of the standard growth curve to the left of the axis of ordinates and the axis of abscissae. It is a condition for the correctness of the method that the curves actually follow a rectilinear course to the left of the axis of ordinates. That the curves do this cannot be proved, but is here assumed. This being so, the author has been afraid to employ the method in his extensive investigation on the vitamin B<sub>1</sub> content of blood in normal and diseased persons (published elsewhere), but has instead used Meiklejohn's method of estimation, well aware that this method is encumbered with errors.

### 3. The errors of the *Phycomyces* method.

These errors may be classified as 1) the error involved in estimating the vitamin B<sub>1</sub> content of the blood according to Meiklejohn's method without taking into account the adjuvant factor of the blood, and 2) the «statistical» errors of the method itself. In the following these errors will be discussed briefly.

1. In a series of experiments the author has tried to get an idea of how often and to what degree the blood produces an effect on the fungus growth that is not attributable to its vitamin B<sub>1</sub> content. The standard growth curve (the curve plotted on the basis of the growth in flasks with known, increasing amounts of vitamin B<sub>1</sub>, and which is used at the interpolation with the dry weight in flasks with blood) has such a shape that it becomes approximately a straight line when logarithmic values are plotted. The same applies to the curve that may be drawn through points determined by the growth in flasks with blood and in flasks with blood + addition of

vitamin B<sub>1</sub>; very small amounts of vitamin B<sub>1</sub> are used because of the conditions in the medium with respect to nitrogen, see above. If these two curves — the standard growth curve and the «blood growth curve» — have the same slope, it is an indication that the blood only influences the fungus growth because of its vitamin B<sub>1</sub>. Interpolation on the basis of the dry weight of the fungus obtained with such blood (without addition of vitamin B<sub>1</sub>) according to Meiklejohn's method is thus permissible. But if the two curves have significantly different slopes it is actually impossible to estimate the vitamin B<sub>1</sub> content of the blood by interpolation on the standard curve.

Using 16 different blood samples the author has investigated the above mentioned deviation of the slope of the «blood growth curve» from that of the standard growth curve, both plotted as straight lines. The growth is determined in flasks with 1 ml of blood and no vitamin B<sub>1</sub> added, and in flasks with 0.05, 0.075 and/or 0.10 microgram of vitamin B<sub>1</sub> added.

If only one addition of vitamin B<sub>1</sub> is used, the slope of the curves is computed as follows:

$$b' = \frac{y_1 - y_2}{x_1 - x_2}$$

where  $b'$  is the slope of the «blood growth curve»,  $y_1$  and  $y_2$  the mean logarithms of the dry weights corresponding to blood without and with vitamin B<sub>1</sub>, and  $x_1$  and  $x_2$  the logarithms of the vitamin B<sub>1</sub> content of the blood without and with vitamin B<sub>1</sub> added. If  $b$  denotes the slope of the standard growth curve from the same experiment, the difference between the slopes, multiplied by  $(x_1 - x_2)$ , is

$$d = (b' - b) (x_1 - x_2) = y_1 - y_2 - b (x_1 - x_2).$$

The square of the mean error of  $d$  is calculated from the formula

$$ME^2 \{d\} = \sigma^2 \left[ \frac{1}{n_1} + \frac{1}{n_2} + \frac{(x_1 - x_2)^2}{SS_x} \right]$$

where  $\sigma^2$  may be replaced by the estimate of the variance of the standard regression line (= 0.000954, on the basis of 34 standard curves),  $n_1$  and  $n_2$  are the number of observations of growth in the flasks with blood, respectively without and with addition of vita-

Table

The results of 16 experiments on quantitative determination of the (known) titration of the difference between the slope of the standard growth curve found where no vitamin had been added,  $B_1$  (1) the blood —

Blood No.	$y_1$	$y_2$	$\div (y_1 \div y_2)$	$x_1$	$x_2$	$\div (x \div x_2)$	$b$	$d$	$n_1$	$n_2$
1	1.703	1.823	0.120	1.152	1.283	0.131	0.526	0.051	4	2
2	1.690	1.824	0.134	1.124	1.264	0.140	0.526	0.060	4	4
3	1.686	1.744	0.058	1.100	1.246	0.146	0.473	$\div 0.011$	4	4
4	1.694	1.800	0.106	1.117	1.258	0.141	0.473	0.039	4	4
5	1.662	1.830	0.168	1.086	1.236	0.150	0.530	0.088	2	2
6	1.512	1.591	0.079	0.934	1.134	0.200	0.582	$\div 0.037$	2	2
7	1.514	1.624	0.110	0.940	1.137	0.197	0.582	$\div 0.005$	2	2
8	1.439	1.565	0.126	0.806	1.057	0.251	0.582	$\div 0.020$	2	2
9	1.639	1.778	0.139	1.029	1.260	0.231	0.569	$\div 0.008$	3	3
10	1.528	1.709	0.181	0.832	1.155	0.323	0.569	0.003	3	3
11	1.633	1.773	0.140	1.017	1.253	0.236	0.569	0.006	3	3
12	1.633	1.750	0.117	1.017	1.253	0.236	0.569	$\div 0.017$	3	3
13	1.583	1.761	0.178	0.929	1.204	0.275	0.569	0.022	3	3
14	1.577	1.745	0.168	0.919	1.199	0.280	0.569	0.009	3	3
15	1.617	1.728	0.111	0.748	1.025	0.277	0.458	$\div 0.016$	3	3
16	1.640	1.758	0.118	0.799	1.053	0.254	0.458	0.002	3	3

min  $B_1$ , and  $SS_x$  the sum of the squares of  $x$  for the standard curve (the values shown in table 6)

If

$$t = \frac{d}{ME \{d\}} > |1.96|$$

( $t$  the «Student's  $t$ » and  $ME$  the mean error) then there is a significant difference between the slope of the standard growth curve and the slope of the «blood growth curve» (the 5 % limit).

If more than one vitamin  $B_1$  addition is used in the flasks, the formula reads

$$ME^2 \{b' - b\} = \left[ \frac{1}{SS_x} + \frac{1}{SS_x} \right]$$

where  $SS_x$  is the sum of squares of  $x$  for the «blood growth curve».

Table 6 shows that in numerous instances there is good agreement between the results obtained with and without the addition of vitamin  $B_1$  to the flasks with blood. But in several instances

6.  
amount of vitamin B<sub>1</sub> added to flasks with blood, as well as a statistical investigation and the slope of the blood growth curve. B<sub>1</sub>(0) is the blood — vitamin B<sub>1</sub> value vitamin B<sub>1</sub> value found when vitamin had been added.

SK <sub>x</sub>	$\frac{\div (x \div x_2)^2}{SK_x}$	Mr <sup>2</sup> { d }	Mr{ d }	t	B <sub>1</sub> (0)	Vitamin B <sub>1</sub> added	B <sub>1</sub> (1) ÷ Vitamin B <sub>1</sub> added
0.694	0.025	0.000739	0.0272	1.87	13.8	0.05	18.4
0.694	0.028	0.000504	0.0224	2.68	12.9	0.05	18.5
0.627	0.034	0.000509	0.0226	÷ 0.49	12.0	0.05	11.1
0.627	0.032	0.000508	0.0225	1.73	12.5	0.05	16.3
0.391	0.058	0.001009	0.0318	2.77	11.1	0.05	19.1
0.384	0.104	0.001053	0.0324	÷ 1.14	6.0	0.05	4.2
0.384	0.101	0.001050	0.0324	÷ 0.15	6.1	0.05	5.8
0.384	0.164	0.001110	0.0333	÷ 0.60	3.8	0.05	3.0
0.505	0.106	0.000736	0.0271	÷ 0.30	10.3	0.075	10.9
0.505	0.207	0.000833	0.0289	0.10	6.4	0.075	6.3
0.505	0.110	0.000740	0.0272	0.22	10.0	0.075	10.5
0.505	0.110	0.000740	0.0272	÷ 0.62	10.0	0.075	8.9
0.505	0.150	0.000778	0.0279	0.79	8.1	0.075	9.6
0.505	0.155	0.000783	0.0280	0.32	7.9	0.075	8.5
0.492	0.156	0.000784	0.0280	÷ 0.57	4.8	0.05	4.0
0.492	0.131	0.000760	0.0276	0.07	5.5	0.05	5.6

(e.g., Nos. 1, 2, 4 and 5) there is considerable disagreement so that the amount of vitamin B<sub>1</sub> found is larger than the amount added. The statistical investigation of the results shows, too, that there is a significant difference between the slopes of the regression lines (Nos. 2 and 6) while in other cases t is rather close to 1.96 (Nos. 1, 4 and 6). Thus it appears that the disagreement is the greatest in blood with a rather high «spontaneous» vitamin B<sub>1</sub> content, which indicates that perhaps the nitrogen question plays a part, as mentioned before.

The conclusion to be drawn from the above experiments is that while frequently it is so that the vitamin B<sub>1</sub> added to the flasks with blood can be determined quantitatively (taking the experimental error into account), it is nevertheless not infrequent to find considerable disagreement between the amount of vitamin B<sub>1</sub> added and that refound by analysis. Hence we must conclude that also the fungus growth caused by the spontaneous vitamin B<sub>1</sub> content of the blood is influenced, and thus distorted, owing to unknown substances in the blood samples concerned.



2. *The »statistical» error of the method.* The reproducibility of individual analytical results, the validity of the rectilinear regression line, etc., are questions which, according to what has been said, have only limited significance when it remains necessary to reckon with an uncertainty owing to the adjuvant factor of the blood. It should be of some interest, however, to get an idea of the order of magnitude of the »statistical» error, and the question will therefore briefly be discussed.

The variability of the growth results obtained without addition of blood to the flasks was investigated in a large number of experiments. The variability was found to be far greater for the fungus growth produced by the vitamin B<sub>1</sub> addition zero than for the growth produced by large or small additions of vitamin B<sub>1</sub>. It was found (when operating with the logarithm of the dry weights and of the standard variation of the dry weights) that the relative standard variation was independent of the weights. For the vitamin B<sub>1</sub> addition zero it was found, in double determinations, that the error of the determination of the dry weight was from + 42 % to -30 %; for additions of vitamin B<sub>1</sub> greater than zero it was found, in double determinations, that the error was from + 8.4 % to -7.8 % — in other words, the reproducibility was rather satisfactory.

The investigation of the reproducibility of the growth results in the presence of blood showed — on the basis of numerous experiments — that it was practically of the same magnitude as in the experiments where no blood had been added. Adding these errors to that originating from the validity of the rectilinear (logarithmic) standard regression line (determined on the basis of 34 standard curves) one arrives at a value for the practical limits of error of the method (ignoring the uncertainty at the vitamin addition zero) equal to  $\pm 20$  %. This is not an insignificant error, though it cannot be called unreasonable when remembering that one is here dealing with a biological assay.

The results of this investigation on the accuracy of the Phycomyces method do not seem very encouraging. The author did not give up, however, since the values found in his investigations on a large material, including normal and diseased persons, very closely corresponded to what others have found with the use of other methods — especially the cocarboxylase activation method which

at present seems to be the only other useful method for the analysis of blood. The results of the investigations mentioned will be reported elsewhere.

### Summary.

The estimation of vitamin B<sub>1</sub> in a sample of blood is in principle carried out according to the method of Meiklejohn, but with the modification that logarithmic standard growth curves are used, the advantage being that such curves are rectilinear. Formulae for use in the computation are given.

The specificity of the *Phycomyces* test is examined, partly on the basis of available literature, partly through own experiments. It is found that only a few of the molecular groups of the thiamin molecule can be substituted by others. The author's experiments on the possible influence of a series of other substances on the growth of *Phycomyces* (nicotinic acid, riboflavin, adermin, biotin,  $\beta$ -alanine, pantothenic acid, p-amino benzoic acid and inositol) show that biotin alone influences the growth, and then in such a way that it appears to be just as growth-promoting as vitamin B<sub>1</sub>, but that its effect fails to appear when thiamin also is present. Hence, and because the biotin content of human blood is considered to be small, this substance seems to be without any notable influence on the estimation of Vitamin B<sub>1</sub> in blood by the *Phycomyces* method.

A critical examination is made of a method proposed by Sinclair (1939) as correction for the "adjuvant factors" of blood, i.e. the one or several factors in the blood which influence (stimulate) the growth of the fungus without being vitamin B<sub>1</sub>. It is found that the method is not correct, since the amount of nitrogen which is supplied to the medium by addition of blood permits a stronger growth in the flasks with blood than in the flasks of the standard series. It is shown that the fungus in certain instances actually avails itself of the nitrogen introduced by the blood and even then — with the aid of an hypothetical proteolytic enzyme — is capable of splitting off nitrogenous compounds from the blood proteins which have coagulated out at the autoclaving.

The quantitative demonstration of small amounts of vitamin B<sub>1</sub> added to the flasks with blood is possible in some, but not in

all instances. Statistically significant disagreements make it necessary to assume that blood, not only through its vitamin B<sub>1</sub> content, can influence the fungus growth. Thus the *Phycomyces* method does not yield actual values for the vitamin B<sub>1</sub> content of the blood, but values which are designated as »vitamin B<sub>1</sub> equivalents» or »vitamin B<sub>1</sub> indicators».

The numerical material obtained from a number of standard series is subjected to statistical treatment. It is found that the variability of the growth results is far greater when the addition of vitamin B<sub>1</sub> is = 0 than when it is > 0. In the latter case it amounts to + 12 to ÷ 11 % for 1 observation, and + 6 to ÷ 6 % for 4 observations.

### Bibliography.

Bang, H. O.: Nogle Bemærkninger om kvantitativ B<sub>1</sub>-Vitaminbestemmelse i Blod og Urin ved Hjælp af Svampemetoden. (Ref.) *Ugesk. f. Læger* 104: 572, 1942. — Knight, B. C. J. G.: The Nutrition of *Staphylococcus Aureus*. The Activities of Nicotinamide, Aneurin and Related Compounds. *Biochem. J.* 31: 966, 1937. — Kögl, F. & N. Fries: Über den Einfluss von Biotin, Aneurin und Meso-Inosit auf das Wachstum verschiedener Pilzarten. *Ztschr. f. physiol. Chem.* 249: 93, 1937. — Lehmann, J. & H. E. Nielsen: B<sub>1</sub>-Vitaminbestimmung im Blut nach Schopfers *Phycomyces*methode. *Acta med. Scandinav. Supp.* 123: 374, 1941. — Meiklejohn, A. P.: The Estimation of Vitamin B<sub>1</sub> in Blood by a Modification of Schopfer's Test. *Biochem. J.* 31, 1441, 1937. — Nielsen, N. & V. Hartelius: Methode zur Bestimmung kleiner und kleinster Mengen von Biotin in tierischen und pflanzlichen Substanzen. *Compt. rend. d. trav. du lab. Carlsberg, Serie physiol.* 23: 387, 1942. — Ochoa, S. & R. A. Peters: Vitamin B<sub>1</sub> and Cocarboxylase in Animal Tissues. *Biochem. J.* 32: 1501, 1938. — Peters, J. P. & D. D. van Slyke: Quantitative Clinical Chemistry. London 1932 p. 353. — Peters, R. A. & J. R. O'Brien: The Vitamin B-Group. *Annual Rev. Biochem.* 7: 305, 1938. — Reader, V.: Relation of Growth of Certain Micro-Organisms to Composition of Medium. *Biochem. J.* 23: 61, 1929. — Robbins, W. J. & F. Kavanagh: Intermediates of Vitamin B<sub>1</sub> and Growth of *Phycomyces*. *Proc. Nat. Acad. Sc.* 23: 499, 1937. — Robbins, W. J. & F. Kavanagh: The Specificity of Pyrimidine for *Phyc. Blakesleeanus*. *Proc. Nat. Acad. Sc.* 24: 141, 1938. — Robbins, W. H. & F. Kavanagh: The Specificity of Thiazole for *Phyc. Blakesleeanus*. *Proc. Nat. Acad. Sc.* 24: 145, 1938. — Schopfer, W. H.: Recherches sur l'utilisation des facteurs de croissance. *Arch. f. Microbiol.* 6: 196, 1935. — Schopfer, W. H. & A. Jung: Un test végétal pour l'aneurine. V<sup>e</sup> Congrès international technique et chimique des industries agricoles Scheweningue

1937 p. 21. — Schopfer, W. H.: L'action des constituants de l'aneurine sur des levures. *Compt. rend. Acad. d. sc.* 205: 445, 1937. — Schopfer, W. H.: La spécificité d'action de l'aneurine sur *Phycomyces*. *Bull. Soc. botanique suisse* 47: 460, 1937. — Schopfer, W. H.: Vitamine und Wachstumsfaktoren bei den Microorganismen mit bes. Berücksichtigung des Vit. B<sub>1</sub>. *Ergeb. d. Biol.* 16: 1, 1939. — Schopfer, W. H.: Le problème de la spécificité d'action des vitamines. *Compt. rend. Soc. physique et d'histoire naturelle de Genève* 58: 58, 1941. — Sinclair, H. M.: The Estimation of Vitamin B<sub>1</sub> in Blood. *Biochem. J.* 32: 2185, 1938. — Sinclair H. M.: The Estimation of Vitamin B<sub>1</sub> in Blood. A Further Modification of Meiklejohn's Method. *Biochem. J.* 33: 2027, 1939. — Wassink, E. C.: Begrenzende Bedingungen bei der Atmung von *Phycomyces*. *Recueil des trav. botaniques néerland.* 31: 583, 1934. — Westenbrink, H. G. J. et al.: The Determination of Aneurinpyrophosphat in Blood. *Zeitschr. f. Vitaminforsch.* 13: 218, 1943.

---

From the Medical Clinic A of the University of Copenhagen, the  
Rigshospital. (Chief: Professor Carl Sonne, M. D.)

## Oscillometric Studies.

On the Change of Sensitivity of the Oscillometer at the Different Pressures, and on the Influence of the State of Contraction of the Arterial Wall on the Oscillometric Curve.<sup>1</sup>

By

B. CHR. CHRISTENSEN, M. D.

(Submitted for publication June 6, 1944.)

---

By the oscillatory method one measures the pulsatory oscillations of the arterial wall against a varied pressure from without.

Numerous theories have been advanced in the course of time as to the conditions during the oscillometric measuring. In the author's opinion the most intelligible statement has been given by Plesch (1935), whose explanation will in the main be followed here.

Before an account is given of Plesch's theory it should be mentioned that by the compression pressure of an artery we understand the pressure that a pressure from without must exceed the one existing in the artery to change the cross-section of the artery from a circle to the shape of a band with canals along the border.

Janeway & Park (1910) have studied the compression pressure of fresh ox-arteries and found that at a normal tone of the wall it is about 10 mm Hg, and that a maximally contracted artery has a compression pressure of about 30 mm Hg. Unfortunately they have stated nothing as to the relation between the volume of the artery and the compression pressure. This relation, which may be

---

<sup>1</sup> The investigations have been carried out with financial support from the Kong Christian den Tiendes Fund.

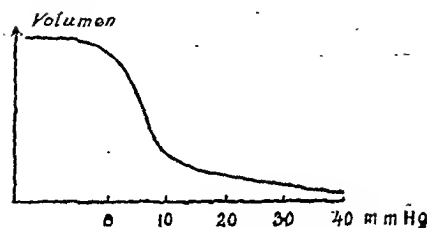


Fig. 1. Pressure-volume curve from an artery-like rubber tube 6.5 mm in clear diameter and with a thickness of the wall of 0.5 mm. The abscissa indicates the difference between the pressure from without and that from within in mmHg, the ordinate indicates the change of volume. (After Plesch, 1935).

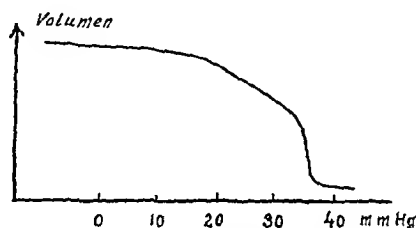


Fig. 2. Pressure-volume curve from an artery-like rubber tube 5.5 mm in clear diameter and with a thickness of the wall of 0.75 mm. The abscissa indicates the difference between the pressure from without and that from within in mm Hg, the ordinate indicates the change of volume. (After Plesch, 1935).

indicated in a pressure-volume curve with the compression pressure as abscissa and the volume or the lumen of the artery as ordinate, has been examined with regard to «artery-like rubber tubes» by A. Müller (1929), Eldahl (1933) and Plesch (1935). The pressure-volume curves found by these investigators are all of the same shape. A single one of these curves, the one from Plesch's works, is rendered here (fig. 1). If we examine next the pressure-volume curve of a thick-walled rubber tube, which is meant to correspond to a thick-walled or contracted artery, it appears that the shape of the curve is altered but little, as may be seen from fig. 2, likewise from Plesch's works.

A. Müller states that an excess pressure from without of 5 mm Hg is capable of flattening the radial artery in man, and that an excess pressure of 10 mm Hg compresses it leaving only small canals along the borders, which means that the radial artery of man has a compression pressure of 10 mm Hg.

If an extremital artery is compressed by means of a circular pneumatic cuff with a pressure exceeding the systolic pressure +

the compression pressure of the arterial wall the artery will become almost totally compressed during both systole and diastole, and there can be measured no pulsatory oscillations worth mentioning. If the pressure is lowered to a value lying below the systolic pressure + the compression pressure of the arterial wall, but above the systolic pressure, the artery will in each systole be dilated for a brief moment corresponding to the difference between the pressure in the cuff and the systolic pressure + the compression pressure. A cuff pressure amounting to the same as the systolic pressure will make the artery entirely compressed during the diastole and circular in cross-section at the moment the systolic pressure exists in the artery. If now the pressure from without decreases so much as to lie below the systolic pressure but above the diastolic pressure + the compression pressure of the arterial wall, the artery will be entirely compressed in the diastole and more and more dilated during the systole corresponding to the ever increasing difference between the pressure from without and that from within and the resulting ever increasing dilatation of the elastic artery. Then on lowering the pressure below the diastolic pressure + the compression pressure the artery will no longer be totally compressed during the diastole, but will, gradually as the pressure decreases, become more and more dilated. In other words by a change of pressure from diastole to systole it will oscillate between a more or less compressed form and a circular form. If now the pressure from without falls below the diastolic pressure, the artery will also during diastole have a circular cross-section and be more or less dilated dependent on the variations of the pressure from within. It appears from the above that the relations of the oscillations of the arterial wall at the different pressures from without must depend partly on the difference between diastolic and systolic pressure and partly on the conditions of compression of the arterial wall.

An artery must during both systole and diastole dilate against a decreasing pressure from without corresponding to the pressure-volume curve of the wall, and the pulsatory oscillations occurring at a certain pressure from without must arise as a result of the change from diastolic to systolic pressure-volume-curve. This fact is found illustrated in fig. 3, in which the 2 curves indicate a systolic and a diastolic pressure-volume curve respectively. The ordinate

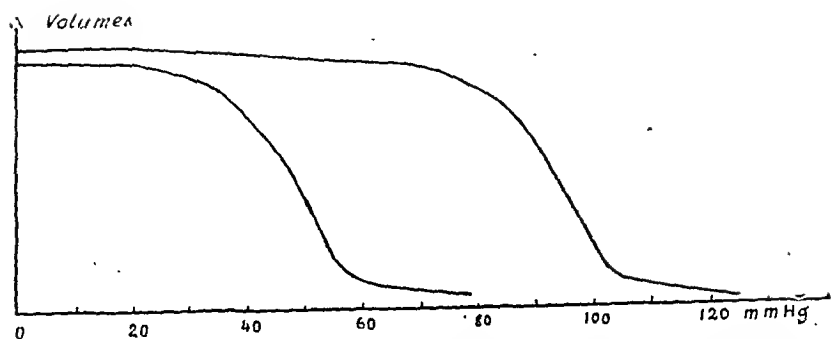


Fig. 3. Normal artery. Systolic and diastolic pressure-volume curve. The abscissa indicates the pressure from without in mm Hg, the ordinate indicates the change of volume.

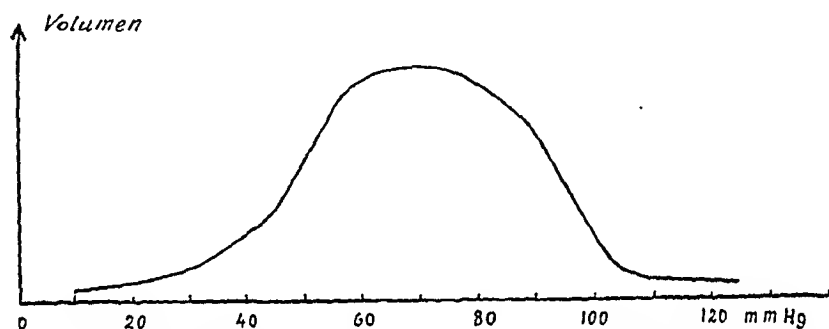


Fig. 4. A constructed oscillometric curve on the basis of fig. 3. The abscissa indicates the pressure from without in mm Hg, the ordinate indicates the change of volume.

differences must indicate the pulsatory oscillations and must, if they are entered in a co-ordinate system with the pressure as abscissa and the oscillations as ordinate, give a so-called oscillometric curve. This is shown in fig. 4.

It appears from the theoretical considerations that the oscillometric curve must be symmetrical with regard to its summit, as both the systolic ascending and the diastolic descending part are caused by the pressure-volume curve of the arterial wall. The curve constructed here complies with these conditions, but the ordinary oscillometric measurements show different facts.

Thus Dan Prytz (1942), who applied an optically registering oscillograph in connection with Gallavardin's double cuff, has found, after a statistic treatment of a very great number of measurements, that the ascending part of the oscillometric curve covers a much larger pressure area than the descending part. By



measuring on the brachium we get an average difference of about 20 mm Hg, and by measuring on the femur of about 35 mm Hg. In Prytz' opinion the cause of this difference is to be sought in the fact that during the measurement with a decreasing pressure in the cuff there occurs a fall in the blood pressure at the moment the flood through the compressed part of the artery begins.

Prytz pays no regard to the fact that the sensitivity of the oscillometer increases at a decreasing pressure, a fact to which Eldahl (1933) has given attention, but which has not previously been investigated.

### Own Investigations,

The oscillometric study consists actually in a plethysmographic measurement of the cross section of an extremity. A change of volume in the extremity brings about a pressure variation in the oscillometer, which roughly speaking consists of a pneumatic cuff, rubber tubes, and a differential manometer. It follows from this that the pneumatic cuff must have the same volume at all pressures if the oscillometer shall have an unchanging sensitivity. This is, however, not the case, as the volume of the cuff increases at an increasing pressure, from which it follows that its sensitivity will decline. The size of this change of volume has not previously been investigated. As, however, this variation must be of great importance for the estimation of the oscillometric curve, the author has undertaken such measurements by means of an optically registering oscillograph in connection with the usually applied Gallavardin's double cuff.

In the following a brief description will be given of the apparatus (fig. 5). The volume oscillations are registered optically by means of a differential manometer (D) in which a narrow mirror (S) is placed on the rubber membrane. The differential manometer has uninterrupted connection with the distal cuff of the Gallavardin cuff. The outer room has connection with the distributor cock (F.H.) by a glass air-chamber (V) of about 300 cm<sup>3</sup>, which is to prevent oscillations in the membrane from causing pressure variations in the outer room. Further the cock has connection with the proximal cuff of the Gallavardin cuff, a Hg manometer (M), and a compressed-air holder.

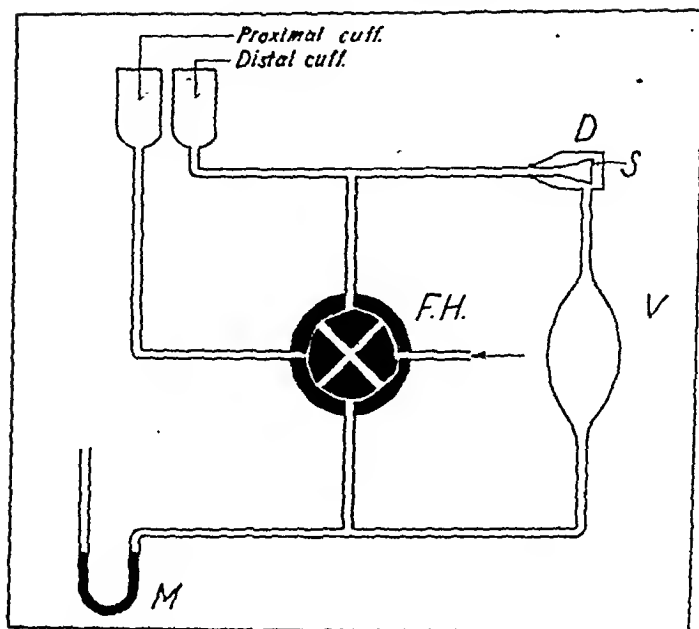


Fig. 5. Outline drawing of the oscillograph used by the author. For explanation see text.

When the cock is placed as illustrated in the figure it cuts off all connections from the different parts of the apparatus to the connection between the distal cuff and the differential manometer. If turned  $45^\circ$  it makes a connection between both cuffs in the Gallavardin cuff and the differential manometer. The sensitivity of the differential manometer is the same at all pressures.

The essential part of the registering manometer in this oscillograph is the rubber membrane in the differential manometer. It has appeared that the sensitivity of the manometer must be so great that a volume increase of 0.50 ml in an empty, fastened cuff must give an oscillation of the optic index of 35 to 40 mm. If the oscillation is smaller all curves will be drawn flat so that it will be impossible to see plainly changes in the shape of the oscillometric curve.

The measurements were undertaken in the manner that the oscillometric cuff was first placed in the correct way, i. e. smoothly and tightly round the upper arm, after which the pressure in the manometer was pumped up to 200 mm Hg. Next the amounts of air found in the cuff at the different pressures were measured over water and at the existing height of the barometer. By simple reduc-

Table 1.

The volume of the registering cuff at the different pressures.

mm Hg in the cuff	ml air in the cuff
200	103
190	102
180	99
170	98
160	95
150	94
140	91
130	87
120	85
110	82
100	79
90	73
80	67
70	60
60	54
50	48
40	41
30	32
20	25
10	15
0	10

tion according to the equation of condition of the gases it was then possible to determine the cuff volume at the different pressures.

As a great number of measurements presented identical variations, only the values from a single experiment will be rendered here (table 1).

In order to get an impression of the sensitivity of the oscillogram a calculation was made next of the increase in pressure arising in the cuff when the volume of the latter is decreased by 1 ml. The values of these increases in pressure are indicated in fig. 6, which thus gives expression to the change of sensitivity of the oscillogram within the pressure area of 0 to 200 mm Hg. It appears from fig. 6 that at decreasing pressures the sensitivity increases smoothly and quite inconsiderably from 200 to 100 mm Hg. From 100 to 40 mm Hg the sensitivity increases about 100 per cent. Under 40 mm Hg there is a very great increase in the sensitivity.

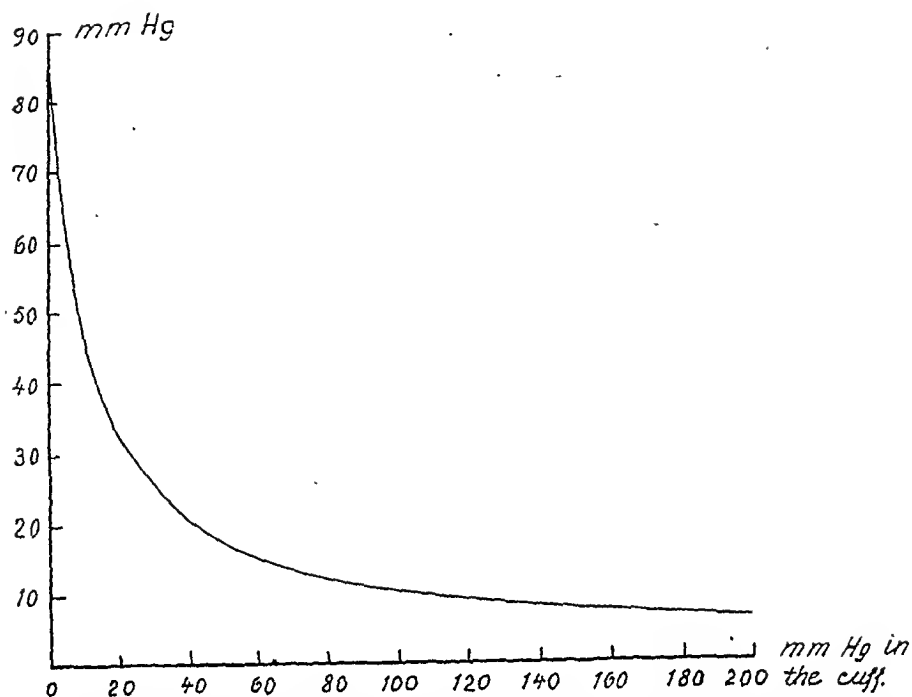


Fig. 6. Variation in sensitivity of the oscillometer. The abscissa indicates mm Hg in the cuff. The ordinate indicates the calculated pressure increase when the volume of the cuff is decreased 1 ml at the different pressures.

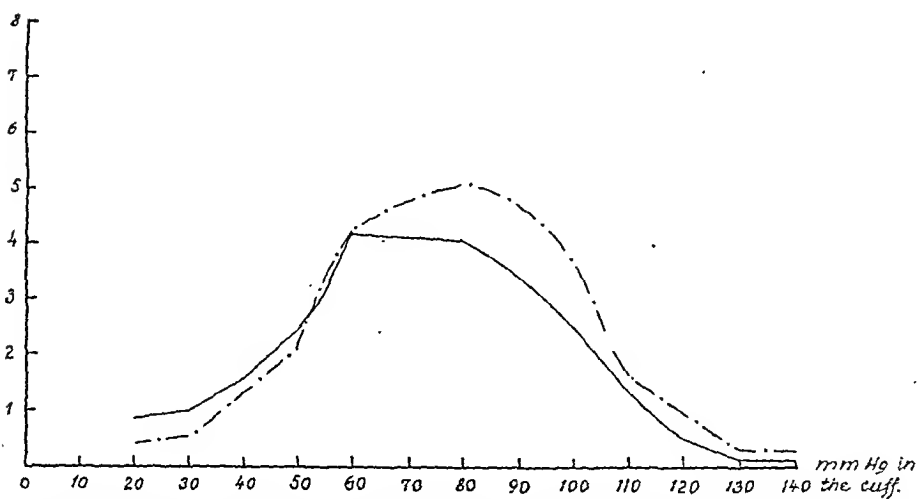


Fig. 7. 2 oscillometric curves. The abscissa indicates the mm Hg in the cuff. The ordinate indicates the oscillations of the index of the oscillometer expressed in mm. The fully drawn curve is the one registered, the dotted curve is the theoretic curve calculated on the basis of the variation of sensitivity

A so pronounced variation in the sensitivity must cause a misdrawing of the oscillometric curve in such a manner that the summit of the curve is registered at a lower pressure than that at which it is actually found. In illustration of this fact fig. 7 renders an oscillometric curve, such as it has been registered by the oscillograph, together with the same curve as it would appear if the oscillograph were equally sensitive at all pressures. The fully drawn line indicates the registered curve, and the dotted curve shows the registering calculated from the presupposition that the oscillograph has the same sensitivity at all pressures, in this case the sensitivity at the registering of the maximal oscillation.

Fig. 7 shows that in reality the summit lies at 80 mm Hg and not as registered at 60 mm Hg. At the same time it is seen that the registered difference between the ascending systolic and the descending diastolic part is decreased, so that the reduced oscillometric curve is practically symmetrical with regard to the summit, as were also to be expected from Plesch's theory.

The greater divergence demonstrated by Prytz by measuring on the femur may be explained by the fact that the femur cuff, which is much larger than the arm cuff, displays a still greater variation of sensitivity.

Besides the conditions mentioned here, which come in at all oscillometric measurements, also alterations in the states of contraction of the artery and in the pressure conditions may bring changes in the shape of the oscillometric curve.

It is seen from fig. 3 that the oscillometric curve changes its shape at the moment the pulse amplitude either increases or decreases. If the amplitude increases, i. e. the 2 pressure-volume curves are removed from each other, the oscillometric curve keeps its height, only instead of having a summit it gets a plateau varying in breadth dependent on the greatness of the amplitude. In consequence of the previously mentioned change of the sensitivity of the oscillograph no plateau is registered as a plateau but as a steadily rising curve. A decreased amplitude, which means that the 2 pressure-volume curves to a greater extent overlap each other's abscissa areas, i.e. the curve extends only over a smaller abscissa areas.

If the lumen of the artery is diminished on account of contraction of the arterial wall the pressure-volume curve will become lower, its height being simply expressive of how much a piece of an

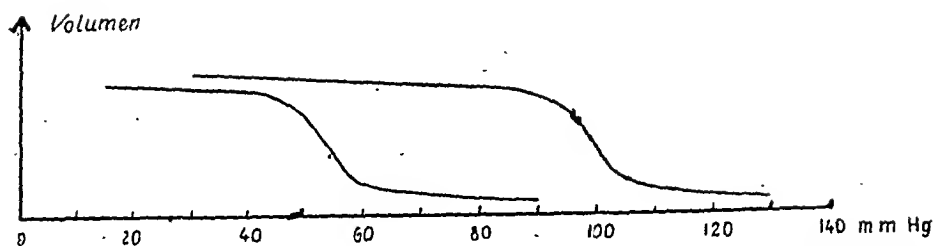


Fig. 8. Artery with contracted wall, normal pulse amplitude. Systolic and diastolic pressure-volume curves. The abscissa indicates pressure from without in mm Hg, the ordinate indicates the change of volume.

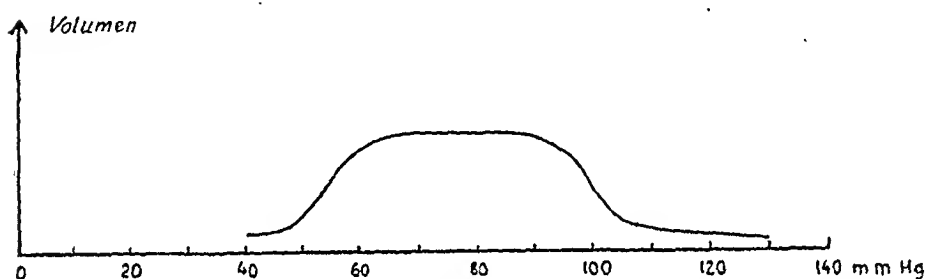


Fig. 9. Constructed oscillographic curve on the basis of fig. 8. The abscissa indicates pressure from without in mm Hg, the ordinate indicates the change of volume.

artery contains when not compressed. It is impossible to say with certainty whether the curve becomes also less steep, but oscillographic curves registered on constricted arteries are not indicative that this should be the case, and Plesch's pressure-volume curves from thickwalled rubber tubes are roughly of the same shape as those obtained by using thin tubes. Supposing now that the pressure-volume curve of the contracted artery is in the main of the same shape as that of the normal one, an artery with a contracted wall and with normal pulse amplitude will be found to have the systolic and diastolic pressure-volume curves indicated in fig. 8. If an oscillographic curve is calculated from the ordinate differences the result will be the curve of fig. 9. The curve is lower than the normal one, which indicates that the lumen of the artery is smaller. Moreover it has got a steadily rising plateau, as the 2 pressure-volume curves are somewhat removed from each other's abscissa areas.

## Summary.

A brief review is given of the theory of the oscillometric curve, based chiefly on Plesch's works. Next it is pointed out that according to Plesch's theory the oscillometric curve should be symmetrical, i.e. the systolic ascending and the diastolic descending parts should be equally great. This is, however, not the case at the measurements. The author calls attention to the fact that the sensitivity of the oscillometer increases at decreasing pressures, and he demonstrates experimentally that the sensitivity is greatly increased at changes of pressure from 100 mm Hg downwards. A registered oscillometric curve is corrected on the basis of an experimentally found curve indicating the sensitivity of the oscilometer. After the correction the curve is symmetrical, as it should be according to Plesch's theory. This goes to show that Plesch's theory of the rise of the oscillometric curve is right.

Finally a brief report is given of the variations in the ordinary curve shape caused by alterations of pressure and of the state of contraction of the arterial wall.

## References.

- 1) Eldahl, A.: Investigations into the oscillatory method, København 1933. (Dissert.) — 2) Janeway, T. C. & E. A. Park: Arch. Int. Med. 6, 586, 1910. — 3) Müller, Aloys: Ztschr. f. d. ges. exper. Med. 67, 698, 1929. — 4) Plesch, J.: Tonoszillografische Blutdruckmessung und die Deutung der Blutdruckkurve, in Abderhalden, E.: Handbuch der biologischen Arbeitsmethoden. Abt. V, Teil 8, Berlin 1935, p. p. 788—803. — 5) Prytz, Dan: Klinisk Blodtryksmaaling. København 1942. (Dissert.).
-

From the Medical Clinic A of the University of Copenhagen, the Rigshospital. (Chief: Professor Carl Sonne, M. D.).

## Studies on Hyperventilation.

### I. Influence of the Carbon Dioxide Tension in the Arterial Blood on the State of Contraction of the Large Arteries in Man.<sup>1</sup>

By

B. CHR. CHRISTENSEN, M. D.

(Submitted for publication June 6, 1944).

---

The CO<sub>2</sub>-tension of the arterial blood influences the state of contraction of the large arteries in two fundamentally different ways: partly it affects the tone of the vasomotor centres, and partly it influences the musculature of the arterial wall itself.

### Previous Investigations on Animals.

Bayliss (1901) has by experiments of perfusion demonstrated the fact that increased amounts of CO<sub>2</sub> in the perfusion-fluid increases the rate of the flow in a frog extremity, but he has not succeeded in demonstrating a corresponding effect of asphyctic, CO<sub>2</sub>-containing blood in extremities of mammals.

Anrep (1912) has proved by plethysmographic measurements that asphyxia brings about vasodilatation in denervated extremities of mammals. Moreover, by experiments of perfusion on isolated rabbit's ears he has demonstrated a considerable acceleration of the flow, when the perfusion fluid contains lactic acid, acetic acid, or hydrochloric acid, and when it contains carbon dioxide.

Schwarz & Lemberger (1911) have studied the flow through

---

<sup>1</sup> The investigations have been carried out with financial support from the Kong Christian den Tiendes Fund.



the submaxillary gland of anesthetized cats after transection of the chorda tympani and the jugular sympathetic nerve. Through these experiments they have succeeded in demonstrating an increase in the rate of the flow when the animal's blood was rich in carbon dioxide on account of respiration in carbon-dioxide-containing air.

Itami (1912) has proved, by experiments on anesthetized intact dogs, cats, and rabbits, that during the respiration in  $\text{CO}_2$ -containing air there occurs a plethysmographically demonstrable vasoconstriction in the upper extremities, and that the impulses of this constriction are led through the sympathetic nervous system to the extremity.

Dale & Evans (1922) have observed, by experiments on anesthetized cats, that hyperventilation with release of  $\text{CO}_2$  brings about an instantaneously occurring fall in the blood pressure. This is in their opinion due to the fact that the  $\text{CO}_2$ -tension irritates the vasomotor centres both in the medulla oblongata and in the medulla spinalis. Furthermore they have demonstrated the fact that injection of sodium bicarbonate has the same effect as respiration in  $\text{CO}_2$ -containing air, which means that it must be the  $\text{CO}_2$  as such and not a shift of the reaction of the blood towards the acid side that affects the vasomotor centres.

Through the plethysmographic measurements we are informed of the state of contraction of the whole vascular system in the extremity in question, whereas investigations into the rate of the flow give information almost exclusively on the conditions in the arterioles the main resistance being found in these vessels.

The above-mentioned investigations of the conditions in isolated organs show that  $\text{CO}_2$  by direct influence brings about a dilatation of the arterioles and perhaps of the arteries.

The investigations made by Itami and Dale & Evans go to show that the stimulating effect of the carbon dioxide on the vasoconstrictive centres of the intact animals is stronger than the peripheral vasodilating effect demonstrated by Bayliss, Anrep, and Schwarz & Lemberger.

Yandell Henderson (1910) on the other hand has observed that in anesthetized cats the femoral as well as the mesenteric arteries are contracted considerably in connection with hyperventilation.

In other words the various experiments on animals have not brought a final solution to the question whether  $\text{CO}_2$  in the living organism has a chiefly central vasoconstrictive or a chiefly peripheral vasodilatative effect.

### Previous Investigations on Humans.

In humans it is possible by means of oseillometric measurements to study the state of contraction of the main arteries in the extremity in question. Investigations a. o. by A. Eldahl (1941) and B. Chr. Christensen & P. Schultzer (1941) have shown that only pulsatory oseillations of the main artery in the extremity are registered by the oseillometric measurement.

R. Marthinsen (1934), who has made hyperventilation experiments on normal humans, has by oscillometric measurements demonstrated a flattening of the oseillometric curve, which he believes to be due to a vasoconstriction caused by the hyperventilation and the resulting reduction of the  $\text{CO}_2$ -tension of the arterial blood.

Also Munch-Petersen (1935) has by hyperventilation shown a similar change in patients with organic cerebral affections. But at the same time he suggests that he has found a corresponding change at hypernicitation, for which reason he is of opinion, unlike R. Marthinsen, that the cause is to be sought in an increased tone in the sympathetic centres caused by a constant voluntary depression of a normal reflex.

In case now the cause is the one suggested by Munch-Petersen it should be possible to bring about the arterial constriction both by prolonged, deep hyperventilation and by shallow, quick ventilation, if both types of ventilation break the normal respiration rhythm and are kept at work voluntarily for some length of time.

### Own Investigations.

In order to investigate further this question the author has made oscillometric measurements by means of a frequently adjusted Paehon's oseillometer on 6 normal persons. In all cases there have been made double experiments.

A description of the oseillometric method and the variations in the arterial pressure and in the state of the vascular wall that

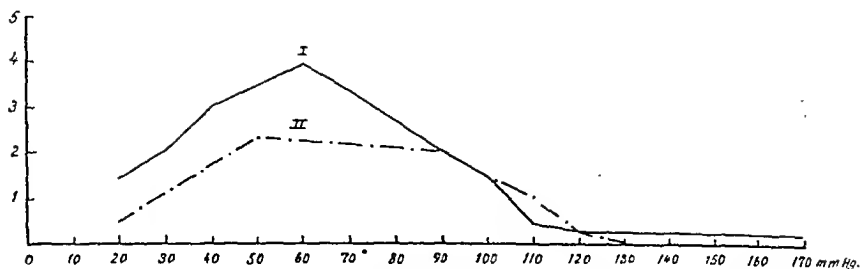


Fig. 1.

change the shape of the oscillometric curve has been given in a previous work by the author (1944).

The influence of both the prolonged, deep and the shallow, quick ventilation was studied. At the experiments with the prolonged, deep ventilation the person experimented on breathed in time to a metronome with a frequency of  $10 \frac{1}{2}$  per minute. At the shallow, quick ventilation, at which it is not known whether the person hyperventilates, the person in question was instructed to breathe all the time «like a dog out of breath», and during the whole experiment care was taken that he ventilated voluntarily.

The person to be experimented on was placed in a sitting posture with the lower extremities stretched out horizontally and with no articles of dress being too tight on the trunk or the lower extremities. He remained sitting in this posture until 2 consecutive oscillometric measurements gave the same result. The respiration experiment was started next. The prolonged, deep respiration lasted until a definite change had occurred in the oscillometric curve, which happened after 5 to 8 minutes of hyperventilation. The experiments with the shallow, quick respiration lasted 15 to 20 minutes.

The experiments showed that there always occurred arterial constriction at prolonged, deep respiration, whereas the shallow, quick respiration, which required considerably more effort of will, caused no flattening of the oscillometric curve.

As an example of the changed shape of curve 2 oscillometric curves will be rendered here from an experiment with prolonged, deep respiration (fig. 1). Curve I was made before and curve II during the hyperventilation. It is plain to see that curve II has got the shape characteristic of a contracted artery.

Thus it appears from these investigations that oseillometrically demonstrable arterial constrictions occur only at a ventilation that favours the release of carbon dioxide.

The change in the shape of the oseillometric curve occurred in all cases long before the appearance of subjective acapnial symptoms.

In none of the experiments mentioned here there has been observed apnea after the hyperventilation, though in some of the cases there appeared acapnial symptoms during the hyperventilation.

In connection with these experiments mention should be made of some investigations made on patients who had become severely anemic as a result of repeated profuse hematemeses.

These patients (there were 3 of them), being hyperpneic on account of the deep anemia, presented on entry a distinctly flattened oseillometric curve with normal arterial pressures. Gradually as the anemia and the hyperpnea vanished the oscillometric curve became normal.

In order to make out whether it were possible to reproduce in normals the arterial contraction in connection with hypernietitation demonstrated by Munch-Petersen in patients with organic cerebral affections, hypernietitation experiments were made on the 6 persons mentioned in the preceeding.

These experiments were made in the same manner as the hyperventilation experiments. The person experimented on was watched carefully all the time and ordered to blink to rapid time. In none of the cases did there occur any flattening of the oscillometric curve. A careful observation during the experiments of the persons disclosed in a few cases a slight, involuntary hyperventilation.

### Conclusion.

The oseillometric investigations undertaken by the author under different forms of changed ventilation show that each ventilation favouring release of the  $\text{CO}_2$  of the blood brings about a contraction of the large arteries of the extremities. Also the hyperpnea attending a severe anemia induces a markedly demonstrable arterial constriction.

Thus the theory advanced by Munch-Petersen cannot be borne out. In the author's opinion the explanation of the arterial constrict-

tion during the hypernictitation may be that the patients in question hyperventilated involuntarily during the experiment.

As in all cases the oscillometrically demonstrable arterial constriction can be registered long before the occurrence of subjective acapnial symptoms, the author is of opinion that the state of contraction of the arteries is a fine indicator of the  $\text{CO}_2$ -tension of the arterial blood.

### Summary.

The author has, by means of oscillometric measurements, studied the state of contraction of the large extremital arteries under different respiratory conditions and found that any type of ventilation causing release of  $\text{CO}_2$  and a resulting reduction in the  $\text{CO}_2$ -tension of the arterial blood brings about a marked arterial constriction. This arterial constriction occurs before the appearance of subjective acapnial symptoms, so accordingly the author is of opinion that the state of contraction of the large arteries is a fine indicator of the  $\text{CO}_2$ -tension of the arterial blood.

### References.

- 1) von Anrep, G.: J. Physiol., 45: 318, 1912. — 2) Bayliss W. M.: J. Physiol. 26: p. XXXII, 1901. — 3) Christensen, B. Chr.: Acta Med. Scandinav. CXX, 474, 1945. — 4) Christensen, B. Chr. & Poul Schultzer: Acta Med. Scandinav 109, 31, 1941. — 5) Dale, H. H. & C. Lovatt Evans: J. Physiol. 56: 126, 1922. — 6) Henderson, Yandell: Am. J. Physiol., 27: 152, 1910. — 7) Itami, S.: J. Physiol., 45: 338, 1912. — 8) Marthinsen, R.: Nord. Med. Tidsskr. 7: 838, 1934. — 9) Munch-Petersen, C. J.: Abstracts of 2. Internat. Neurolog. Congress. London. 1935, p. 85. — 10) Schwarz, Carl & Frieda Lemberger: Arch. f.d. ges. Physiol., 141: 149, 1911.
-

Aus der I. medizinischen Klinik der Universität Helsinki; Vorstand  
Prof. Arvo Vesa.

## Klinische Untersuchungen über die Polyzythämie. I.

Von

MARTTI HIRVONEN.

(Bei der Redaktion am 11. September 1944 eingegangen).

---

Wir sind gewohnt, die normale Zahl der roten Blutkörperchen bei den Männern auf 5 Millionen und bei den Frauen auf 4.5 Millionen Zellen im Kubikmillimeter Blut zu schätzen. Diese Werte sind jedoch Mittelwerte von Normalzahlen, und wir können daher nicht ohne weiteres annehmen, dass Anämie vorliegt, sobald die Zahl der roten Blutkörperchen die genannten Zahlen unterschreitet, wie wir die Menge der Erythrozyten auch nicht als zu gross betrachten dürfen, sobald die genannten Zahlen überschritten sind. Wie bei allen biologischen Zahlenwerten gibt es auch hier Grenzwerte, bei denen die zwischenliegenden Werte als normal anzusehen sind. Von diesen Grenzwerten sind nach Wintrobe bei den Männern als untere Grenze 4.6 Millionen und als obere Grenze 6.2 Millionen sowie bei den Frauen entsprechend 4.2 und 5.4 Millionen zu betrachten. Der obere Grenzwert liegt mithin nach ihm bedeutend weiter von dem Mittelwert entfernt als die untere Grenze. Die Zahlen 6.2 und 5.4 Millionen haben Harrop und Wintrobe bei der Behandlung der Polyzythämie in dem grossen Handbuch der Hämatologie von Downey als untere Grenze der sicheren Polyzythämie aufgefasst. Zu einem ähnlichen Ergebnis ist auch Schulten gekommen, obgleich er keine präzisen Grenzwerte der nor-

malen Zahlen der roten Blutkörperchen angibt, aber er fordert dazu auf, bei der Herleitung von Schlüssen über die erhöhte Zahl der Erythrozyten vorsichtig zu sein, wenn die Menge um 6 Millionen herum bleibt oder kleiner ist.

Die Krankheit, bei der ungewöhnlich viel rote Blutkörperchen und oft auch ungewöhnlich viel andere Blutkörperchen vorkommen, ist mit verschiedenen Namen belegt worden. Die häufigsten Bezeichnungen sind Polycythaemia vera und Erythraemie, wenn die Ätiologie und die Pathogenese der Krankheit unbekannt sind. Der Ausdruck Polycythaemia vera, welcher angibt, dass das Blut viel oder also mehr als gewöhnlich Zellen enthält, wird besonders im deutschen Schrifttum gebraucht. Die in der angelsächsischen Literatur vorherrschende Bezeichnung Erythraemic ist früher auch im deutschen Schrifttum angewandt worden. Zuerst begannen sie Türk und Hirschfeld analog mit der allgemein üblichen Benennung Leukämie zu benutzen. Heute ist sie jedoch ganz aus dem deutschen Schrifttum verschwunden. Der Name Erythraemie, der nach dem Wort Erythrozyt gebildet ist, eignet sich meines Erachtens nicht so gut zur Bezeichnung des in Rede stehenden Krankheitsbildes, da in diesem meist auch eine Vermehrung der Zahl der weissen Blutkörperchen und oft auch eine Zunahme der Zahl der anderen Zellformen zu finden ist.

Die Erhöhung der Erythrozytenzahl aus irgendeiner bekannten Ursache ist andererseits im allgemeinen als Polyglobulie oder Erythrozytose bezeichnet worden. Der Ausdruck Polyglobulie ist von globus abgeleitet, da die roten Blutkörperchen aber nicht kugelförmig sind und da man auch bei diesen Krankheitsformen manchmal, wenschon seltener als bei der erstgenannten kryptogenetischen Krankheit, auch eine Vermehrung anderer Blutkörperchen als der Erythrozyten findet, ist der Name Polyglobulie meiner Ansicht nach nicht ganz angebracht. Der Name Erythrozytose hinwieder ist analog dem Ausdruck Leukozytose gebildet, und gegen ihn können dieselben Einwände erhoben werden wie gegen die Bezeichnung Erythrämie.

Nichts hindert uns dagegen meiner Meinung nach, von beiden Krankheitsgruppen zusammen die sehr passende Benennung Polyzythämie zu gebrauchen. Die kryptogenetische und die hinsichtlich ihres Ursprungs bekannte Form können leicht mit Hilfe der Eigenschaftswörter essentialis und symptomatica auseinan-

dergehalten werden, denn wenn die Polyzythämie durch eine bekannte Ursache oder Krankheit ausgelöst wird, ist sie nur ein Symptom dieser Ursache oder Krankheit und keine Krankheit *sui generis*. Die Hinzufügung eines Eigenschaftswortes macht die Bezeichnung der Krankheit meines Erachtens nicht unbeholfener, sind doch von der kryptogenetischen Polyzythämie z. B. auch schon früher die Ausdrücke *Polyeythaemia vera* oder *Polyeythaemia essentialis* gebraucht worden, und die hier angeführten Namen haben überdies den Vorteil, dass aus ihnen schon ohne Erklärung hervorgeht, um welche Krankheit es sich handelt, was dagegen bei der Anwendung der anderen erwähnten Namen nicht der Fall ist. In meiner Darstellung werde ich also die Ausdrücke *Polyeythaemia essentialis* und *Polyeythaemia symptomatica* gebrauchen.

Von den eigentlichen Polyzythämien ist noch die Pseudopolyzythämie zu unterscheiden. Diese besteht in einer nur zufälligen Erhöhung der Blutkörperchenzahl z. B. infolge eines ungewöhnlich grossen Flüssigkeitsverlustes oder davon, dass die Blutreservoirs, vor allem die Milz, aus der einen oder anderen Ursache momentan Reserv Blut in den Kreislauf entleeren. Die Pseudopolyzythämie kann von Natur örtlich sein, wobei oft im peripherischen Kreislauf erhöhte Erythrozytenwerte anzutreffen sind, während sie in den inneren Teilen des Körpers normal sind. Vogel konstatierte 1854 als erster eine solche vorübergehende Erhöhung der Erythrozytenzahl im Zusammenhang mit einem plötzlichen Flüssigkeitsverlust.

*Polyeythaemia symptomatica* ist bei allen Zuständen festgestellt worden, bei denen in den Geweben aus der einen oder anderen Ursache Mangel an Sauerstoff besteht, und sie ist daher einfach als eine durch Sauerstoffmangel verursachte Kompensationsmassregel des Organismus zu betrachten. Sie ist beim Neugeborenen sofort nach der Geburt, in Verbindung mit gewissen kongenitalen Herzfehlern, ebenso bei einigen erworbenen Herzfehlern, bei gewissen den Lungenkreislauf erschwerenden Lungenkrankheiten, bei der Ayerzsehen Krankheit oder der Pulmonalsklerose, bei Personen, die sich in hohen Gebirgsgegenden aufhalten, sowie bei gewissen Vergiftungen nachgewiesen worden. Malassez und Naunyn veröffentlichten erstmals i. J. 1872 Beobachtungen über die *Polyeythaemia symptomatica* bei angeborenen Herzfehlern.



Vaquez hinwieder war der erste, der 1892 Polyzythämie ohne bekannte oder erklärbare Ursache konstatierte und in der Literatur besprach. Nach ihm wird die Polyeythaemia essentialis auch Vaquezsehe Krankheit genannt. Im englischen Schrifttum führt die Krankheit mitunter auch ohne Grund den Namen Oslersche Krankheit, weil die in den Jahren 1903 und 1904 von Osler mitgeteilten Fälle erst allgemeiner die Aufmerksamkeit auf sie lenkten. Vor Osler, aber nach Vaquez, hatten auch schon manche andere Autoren einzelne Fälle von Polyeythaemia essentialis veröffentlicht.

In der finnischen medizinischen Literatur ist die Polyzythämie sehr wenig behandelt worden. R. Ehrström gab 1932 eine Darstellung der pathogenetischen Probleme der Polyzythämie und erörterte zugleich einige der wichtigsten klinischen Befunde auf Grund von sieben Fällen. M. Ch. Ehrström hinwieder veröffentlichte eigene Untersuchungen über die im Zusammenhang mit Herzinsuffizienz vorkommende Erhöhung der Erythrozytenzahl, die jedoch in den von ihm studierten zehn Fällen keinen solchen Grad erreichte, dass man von einer deutlichen Polyzythämie hätte reden können. Seuderling hat ferner zwei von dem Gewöhnlichen abweichende Fälle von Polyzythämie veröffentlicht. Eigentliche klinische Untersuchungen über die Polyzythämie habe ich dagegen in der finnischen Literatur nicht angetroffen.

Auf die Anregung von Professor Arvo Vesa habe ich es daher angezeigt gefunden, die in der I. und II. medizinischen Klinik der Universität Helsinki behandelten Polyzythämiefälle zu sammeln und zu veröffentlichen. Mein Material umfasst alle während der Jahre 1928—1943 in den genannten Kliniken als Polyzythämien gepflegten Fälle. Ausserdem habe ich alle während dieser Zeit in der I. medizinischen Klinik behandelten Patienten berücksichtigt, bei denen die Zahl der roten Blutkörperchen bei den Männern 5 Millionen und bei den Frauen 4.5 Millionen überstieg. Die deutlichen Pseudopolyzythämiefälle, z. B. die Erhöhungen der Erythrozytenzahl etwas über 5 bzw. 4.5 Millionen im Zusammenhang mit Enteritis oder Diabetes, habe ich dagegen nicht beachtet. Das Hämoglobin ist nach Sahli bestimmt worden.

## I. Polycythaemia symptomatica.

Wie oben erwähnt, habe ich zu dieser Gruppe alle Fälle gerechnet, in denen eine deutliche Grundkrankheit vorliegt, die einen Sauerstoffmangel in den Geweben verursacht hat, wodurch dann als Kompensationsmassregel eine Polyzzythämie entstanden ist. Als sichere Polyzzythämiefälle habe ich diejenigen betrachtet, in denen die Zahl der roten Blutkörperchen die von Harrop und Wintrobe angewandten recht hohen Grenzwerte 6.2 Millionen bei Männern und 5.4 Millionen bei Frauen überschreitet. Als getrennte Gruppe führe ich ausserdem die Fälle an, in denen die Erythrozytenzahl bei den Männern höher als 5 Millionen und bei den Frauen höher als 4.5 Millionen, aber niedriger als die Grenzwerte von Harrop und Wintrobe ist, weil es wenigstens in dem finnischen Patientenmaterial recht selten ist, dass die Zahl der roten Blutkörperchen 5 Millionen bei den Männern und 4.5 Millionen bei den Frauen übersteigt. Die so niedrige Ansetzung des Grenzwertes in dieser getrennten Gruppe hat auch darauf beruht, dass ich bei Herzinsuffizienz ziemlich oft nur etwas über diese Grenzwerte hinausgehende Erythrozytenzahlen, die nach der Heilung der Herzinsuffizienz verschwinden, festgestellt habe.

### 1. Die Polycythaemia symptomatica der Neugeborenen.

Die symptomatische Polyzzythämie der Neugeborenen rührt davon her, dass die Oxydation des Blutes durch die Plazenta nicht so effektiv ist wie seine Oxydation in den Lungen, weshalb die Kinder bei der Geburt regelmässig Polyzzythämie aufweisen. Diese Form der Polyzzythämie kann nach der Literatur sogar recht stark ausgeprägt sein, aber im allgemeinen ist sie verhältnismässig leicht. Die höchsten Werte für die Polyzzythämie der Neugeborenen hat Mayers mitgeteilt. Die von ihm untersuchten Fälle beliefen sich auf 41, und die Zahl der roten Blutkörperchen betrug in diesen Fällen 5.06—9.61 Millionen bei einem Mittelwert von 7.63 Millionen. Nach Isaacs sinkt die Erythrozytenzahl bei den Neugeborenen im Verlauf von zwei Wochen schnell auf normale Werte, und diese Senkung beginnt schon während der ersten Stunden des Lebens.

In meinem Material liegen keine Untersuchungen über die Polyzzythämie der Neugeborenen vor.

## 2. Die *Polycythaemia symptomatica* im Zusammenhang mit Herz- und Lungenkrankheiten.

### a. Die durch angeborene Herzfehler verursachte *Polycythaemia symptomatica*.

Bei kongenitalen Herzfehlern ist die *Polycythaemia symptomatica* ein sehr gewöhnliches Symptom und stellt in manchen Fällen einen wesentlichen Teil des Krankheitsbildes dar. Da die normale Oxydation des Blutes in den Lungen nicht bei allen angeborenen Herzfehlern verhindert ist, tritt Sauerstoffmangel in den Geweben und mithin dadurch bedingte *Polycythaemia symptomatica* auch nicht bei allen kongenitalen Herzfehlern auf. Die mangelhafte Oxydation des Blutes beruht in diesen Fällen entweder darauf, dass in die Lungen wegen des Hindernisses im Herzen oder in den Blutgefäßen nur eine kleinere Menge Blut als gewöhnlich kommt, oder darauf, dass sich Venenblut mit dem Arterienblut vermischen kann, wobei auch die Menge des in die Lungen kommenden Blutes abnimmt. In den Lungen selbst treten dagegen bei den kongenitalen Herzfehlern keine Veränderungen auf, die normale Oxydation des Blutes verhindern würden.

Die Blutmenge des Lungenkreislaufes ist vor allem bei der Pulmonalstenose vermindert, wo durch das verengerte Pulmonalostium nur eine kleinere Menge Blut als gewöhnlich in die Lunge gelangt. Infolge hiervon findet sich bei der Pulmonalstenose immer eine bedeutend erhöhte Erythrozytenzahl und im allgemeinen eine so starke Zyanose, dass von der ganzen Krankheit häufig der Name *Morbus coeruleus* gebraucht wird.

In den Fällen von *Ductus Botalli apertus* ist dagegen die Menge des Blutes im Lungenkreislauf nicht herabgesetzt, weil ein Teil des Aortenblutes in diesen Fällen infolge des in der Aorta herrschenden grösseren Druckes in die Pulmonalarterie kommt, sondern sie kann eher etwas vermehrt sein. Unter diesen Umständen möchte man erwarten, dass in den Fällen von *Ductus Botalli apertus* keine Polyzythämie vorkomme. Gleichwohl hat man in diesen Fällen oft wenigstens einen gewissen Grad von Polyzythämie beobachtet. Dieses Ergebnis ist entweder nur so zu erklären, dass der Druck in der rechten Herzkammer und im Lungenkreislauf wegen der Hypertrophie der rechten Herzhälfte höher als in der Aorta angewachsen ist, wobei umgekehrt Blut unmittelbar aus der Lungenarterie in die

Aorta gelangen könnte und die Menge des Blutes im Lungenkreislauf sich infolgedessen verminderte, oder aber so, dass der Patient gleichzeitig einen anderen, übersehenen angeborenen Herzfehler hat, wodurch eine Vermischung von Venenblut mit Arterienblut ermöglicht und so die Blutmenge des Lungenkreislaufes vermindert wird.

Die Hypertrophie der beiden Herzhälften ist in den verschiedenen Fällen von Ventrikelseptumdefekten sehr verschieden. Daher ist es wohlbegreiflich, dass sich in gewissen Fällen dieser Art Venenblut schon im Herzen mit Arterienblut vermischen kann. Alsdann ist das in die Aorta kommende Blut nicht normal oxydiert, da ein Teil von ihm Venenblut ist, und in diesen Fällen setzt ausserdem das mit dem Arterienblut vermischte Venenblut das in die Lungen kommende Blut mengenmässig herab. Diese Faktoren zusammen rufen in den Fällen von Ventrikelseptumdefekt *Polycythaemia symptomatica* hervor.

Die stärkste Zyanose und die grössten Veränderungen der Erythrozytenzahl findet man selbstverständlich bei den kombinierten angeborenen Herzfehlern, bei denen mehrere Faktoren gleichzeitig in derselben Richtung wirken. Nach Harrop und Wintrobe variiert die Zahl der roten Blutkörperchen bei den kongenitalen Herzfehlern im allgemeinen zwischen 7 und 8.5 Millionen, doch steigt sie manchmal bis auf 10 Millionen. Todtenhaupt hat einen derartigen Fall veröffentlicht, in dem die Erythrozytenzahl 13.9 Millionen betrug. Bei der Obduktion konnte in diesem Fall festgestellt werden, dass das gelbe Knochenmark sich vollkommen in rotes Knochenmark verwandelt hatte, was im allgemeinen nur bei *Polyeythaemia essentialis* geschieht.

Zu meinem eigenen Material gehören vier an kongenitalem Herzfehler leidende Patienten, bei denen eine deutliche *Polycythaemia symptomatica* festgestellt wurde. Bei zweien lautete die klinische Diagnose *Defectus septi ventriculorum*, bei einem *Stenosis ostii pulmonalis* und bei einem *Ductus Botalli apertus*. Die hohen Blutwerte des Falles von *Ductus Botalli apertus* lassen jedoch bezweifeln, ob die Diagnose in diesem Fall richtig war, da in den Fällen von *Ductus Botalli apertus* im allgemeinen keine so hohen Blutwerte vorkommen. Sämtliche Patienten verliessen das Krankenhaus mit mehr oder weniger gebesserten Symptomen, so dass die Diagnosen nicht pathologisch sichergestellt worden sind.

Von diesen Fällen war der an Pulmonalstenose leidende eine 23jährige Frau. Ihr Alter war etwas höher als das durchschnittliche Lebensalter der Pulmonalstenosepatienten, nach Uhlenbruck 21.3 Jahre. Die Patienten mit Ventrikelseptumdefekt und die an Ductus Botalli apertus Leidenden leben bekanntlich oft länger. Die Ventrikelseptumdefekt-Patienten meines Materials waren ein 24jähriger Mann und eine 27jährige Frau. Der an Ductus Botalli apertus leidende Patient in meinem Material war hinwieder ein 49jähriger Mann.

Der zweite Septumdefektfall wurde wegen Blutspucken in das Krankenhaus aufgenommen, alle anderen wegen charakteristischer Herzinsuffizienzbeschwerden. Eigentlich klagte keiner über Kopfschmerz, und keiner hatte Blutungen gehabt. Die Menses der Pulmonalstenosepatientin hatten mit 16 Jahren angefangen und 5 Monate vor der Ankunft der Patientin im Krankenhaus aufgehört. Im Krankenhaus wurden keine gynäkologischen Ursachen zu ihrem Ausbleiben festgestellt, das also offenbar infolge der Grundkrankheit eingetreten war. Bei dem Patienten mit Ductus Botalli apertus war das Sprachvermögen 9 Jahre vor der Aufnahme in das Krankenhaus für einige Tage verschwunden gewesen und dann spontan zurückgekehrt.

Der Körperbau des einen Septumdefektpatienten war kräftig, der des anderen schwächlich, bei den beiden anderen war er gewöhnlich. Das Körpergewicht war bei allen im Verhältnis zur Länge recht normal, eher trat bezüglich des Gewichts ein leichtes Minus auf, wie die folgenden Zahlen zeigen: 177 cm—67.8 kg, 163 cm—56.1 kg, 167 cm—55.3 kg und 162 cm—62.1 kg. Bei allen war die Haut im Gesicht, an den Armen und Beinen stark zyanotisch, wie überhaupt in den Fällen von Polycythaemia symptomtica, während die Hautfarbe bei Polycythaemia essentialis im allgemeinen rot ist.

Bei allen wurden leichtere oder ausgeprägtere Zeichen von Herzinsuffizienz konstatiert, und von dem einen Patienten mit Ventrikelseptumdefekt abgesehen, bekamen alle Digitalistherapie. Der Blutdruck war im allgemeinen gewöhnlich, nur bei dem einen Patienten mit Ventrikelseptumdefekt war er deutlich erhöht und schwankte zwischen 165 und 145 mm Hg. Der Blutdruck des anderen Patienten mit Ventrikelseptumdefekt bewegte sich zwischen 120 und 115, der des Ductus Botalli apertus-Patienten zwischen 145 und 135 und der der Pulmonalstenosepatientin zwischen 136 und 125 mm Hg. Die Pulsfrequenz variierte bei einem Patienten von 65 bis 75 in der Minute und bei den drei anderen von 55 bis 65 in der Minute. Die letzteren bekamen entweder Digitalis oder Scillaren. Bei keinem Patienten wurden arteriosklerotische Veränderungen nachgewiesen. Die Milz war bei keinem palpatorisch oder perkussorisch vergrößert.

Die wichtigsten Blutuntersuchungen gebe ich in Tabelle 1 wieder. Die erste Zahl betrifft den niedrigsten Befund während des ganzen Anstaltsaufenthalts, die letzte Zahl den höchsten Wert.

Tabelle 1.

	Alter	Geschlecht	Hb Sahli	Erythrozy- ten Mill.	Färbe- index	Leukozyten	Lympho- zyten %	Lympho- zyten Zahl
1.	24	♂	128—132	7,800—9,900	0.80—0.82	7,600—7,900	33.0	2,607
2.	22	♀	108—110	6,580—7,860	0.70—0.83	5,700—9,200	15.5	1,426
3.	49	♂	125—148	6,020—7,650	0.90—1.01	2,400—4,800	19.0—34.0	874—1,156
4.	27	♀	110	6,620	0.83	11,100	9.0	999

## Diagnosen der Fälle:

- 1 und 4 Defectus septi ventriculorum  
 2 Stenosis ostii pulmonalis  
 3 Ductus Botalli apertus

Das Hämoglobin ist nach Sahli bestimmt, und für die Lymphozyten ist auch die absolute Menge berechnet.

Aus der Tabelle geht hervor, dass die Hämoglobinwerte aller Fälle deutlich angestiegen waren. Der höchste Wert trat bei dem Patienten mit Ductus Botalli apertus auf. Die Fälle sind nach der Zahl der roten Blutkörperchen angeordnet, da deren Zunahme unbedingt das wichtigste Symptom der Krankheit bildet und da ihre Bestimmungsgenauigkeit auch grösser als die des Hämoglobins ist, zumal wenn man die Werte der beiden Kliniken miteinander vergleicht. Von den Blutuntersuchungen sind in der Arbeit nur die an den Patienten in der Universitätsklinik ausgeführten berücksichtigt worden. Die höchste Erythrozytenzahl zeigt sich bei dem einen Patienten mit Ventrikelseptumdefekt und beträgt 9.9 Millionen. Sie gehört zu den höchsten nach Harrop und Wintrobe bei angeborenen Herzfehlern beobachteten Werten. In dem Fall von Ductus Botalli apertus ist der Färbeindex, der nach Sahli berechnet unter 1, bei 0.80 oder etwas mehr, liegen sollte, infolge des relativ hohen Hämoglobinwertes deutlich erhöht. In allen anderen Fällen ist der Färbeindex normal. Die Leukozytenzahl variiert in den verschiedenen Fällen ziemlich beträchtlich. In dem zweiten Fall von Ventrikelseptumdefekt besteht eine leichte, aber doch ganz deutliche Leukozytose, 11,000. In dem Fall von Ductus Botalli apertus hinwieder liegt eine schwache Leukopenie vor. In den beiden übrigen Fällen sind die Zahlen der weissen

Blutkörperchen die gewöhnlichen. Das Lymphozytenprozent schwankt auch recht erheblich, von 9.0 bis 34.0 %. Die kleinsten Werte findet man jedoch in den Fällen, in denen die Gesamtzahl der Leukozyten am grössten ist. Die absolute Menge der Lymphozyten bleibt somit in den verschiedenen Fällen recht gleich. Nach Bloom enthält das Blut 20—25 % Lymphozyten, woraus man als Gesamtzahl der Lymphozyten 1,200—2,000 erhält, wenn man als Zahl der Leukozyten 6,000—8,000 rechnet. In dem einen Fall von Ventrikelseptumdefekt fand sich mithin eine leicht erhöhte Lymphozytenzahl, 2,607, in dem anderen eine etwas erniedrigte, 999. In den beiden anderen Fällen war die Gesamtzahl der Lymphozyten normal.

In den beiden Fällen von Ventrikelseptumdefekt kamen bei der Differenzierung der Leukozyten weder eosinophile noch auch basophile Zellen zum Vorschein. Jugendformen der neutrophilen Zellen und Myelozyten waren ebenfalls nicht zu entdecken. In dem Fall von Pulmonalstenose kamen weder Jugendformen noch Myelozyten vor, Eosinophile fanden sich 1.5 und Basophile 0.5 %, d. h. die gewöhnlichen Werte. In dem Fall von Ductus Botalli apertus wurden einmal 0.5 % Jugendformen der neutrophilen Leukozyten festgestellt, die Zahl der Eosinophilen schwankte zwischen 3.5 und 5.0 %, und Basophile waren 0.5 % vorhanden. Keiner der Patienten hatte Jugendformen der roten Blutkörperchen im Blute.

Der Senkungswert war in sämtlichen Fällen sehr niedrig. Der Wert der ersten Stunde war in den beiden Fällen von Ventrikelseptumdefekt 0 mm, der der zweiten Stunde in dem einen 0 und in dem anderen 1 mm. In dem Fall von Ductus Botalli apertus variierte die Senkung etwas und war minimal 0/0 und maximal nur 1/2 mm. Die Senkung des Pulmonalstenosefalls betrug 0.5/1 mm.

Der Ikterusindex nach Meulengracht wurde nur in dem Fall von Ductus Botalli apertus ausgeführt und war in den Grenzen des Normalen, 1:6.

Von den übrigen Untersuchungen seien noch die Harnuntersuchungen erwähnt. In den Fällen von Ventrikelseptumdefekt enthielt der Harn kein Albumin. In dem Pulmonalstenosefall wurde Eiweiss festgestellt, dessen Menge zwischen 0 und 4.5 ‰ schwankte. Im Sediment wurden nur Leukozyten und Epithelzellen konstatiert, und da die Albuminmenge bei der Heilung der Herzinsuffizienz fast ganz verschwand, beruhte dies wahrscheinlich auf einer Nierenstauung. In dem Fall von Ductus Botalli apertus trat auch Eiweiss auf, dessen Menge sich auf 0.4—2.25 ‰ belief. Im Sediment fanden sich Erythrozyten, Leukozyten, Epithelzellen, granulierte Zylinder und hyaline Zylinder. Der Wert des Reststickstoffes war andauernd erhöht und betrug zwischen 60 und 80 mg %. Das Nierenleiden des Patienten wurde erstmals 4 Jahre vor seiner Aufnahme in das Krankenhaus festgestellt.

Da die Polyzythämie bei den an einem angeborenen Herzfehler Leidenden eine Kompensationsmassregel des Organismus gegen Sauerstoffmangel darstellt, sind direkt auf die Polyzythämie gerichtete therapeutische Massnahmen nicht indiziert, wenn der Zustand des Patienten nicht unmittelbar durch die Polyzythämie beeinträchtigt wird. Da dies nicht der Fall war, wurde bei den Patienten meines Materials als Therapie hauptsächlich auf das Herz gerichtete Behandlung angewandt. Diese ist denn auch als ausserordentlich wichtig zu betrachten, denn wie sich aus meinen weiter unten angeführten Befunden ergibt, erhöht die Herzinsuffizienz oft die Zahl der Erythrozyten recht bedeutend. Alle Patienten meines Materials verliessen das Krankenhaus mit gebesserten Symptomen.

In meinem Material kommen keine an kongenitalem Herzfehler Leidenden vor, bei denen die Zahl der roten Blutkörperchen die Grenzwerte von Harrop und Wintrobe unterschritte, aber doch bei den Männern über 5 Millionen und bei den Frauen über 4.5 Millionen betrüge.

*b. Die durch erworbene Herzfehler verursachte Polycythaemia symptomatrica.*

Von den erworbenen Herzfehlern löst die Mitralstenose nach Harrop und Wintrobe meistens eine Polyzythämie aus. Der Sauerstoffmangel in den Geweben würde dabei gemeinsam durch eine Kreislaufstörung und pathologische Veränderungen in den Lungen verursacht werden. Die Farbe der alsdann auftretenden Zyanose unterscheidet sich nach ihnen von der durch die essentielle Polyzythämie hervorgernenen Farbe der Zyanose, und Leukozytose tritt im allgemeinen nicht auf. Im Zusammenhang mit Aortenfehlern kommt die Polyzythämie nach ihnen viel seltener vor. Über die Rolle der Herzinsuffizienz bei der Entstehung der Polycythaemia symptomatrica geben Harrop und Wintrobe nichts an. M. Ch. Ehrström hat den Stoffwechsel des Blutes und die Urobilinurie bei Herzinsuffizienz studiert und hat dabei feststellen können, dass während der Insuffizienz deutlich eine Neubildung von Blut stattfindet, während nach dem Verschwinden der Insuffizienz eine erhöhte Hämolyse eintritt. Bei einer Patientin unter seinen 10 Fällen ging die Zahl der roten Blutkörperchen während der



Insuffizienz auf 5.56 Millionen herauf. Diese Zahl übersehreitet die von Harrop und Wintrobe aufgestellte untere Grenze der polyzythämischen Werte 5.4 Millionen. In anderen Fällen Ehrströms führte die Blutneubildung während der Insuffizienz nicht zu so hohen Erythrozytenzahlen, und Ehrström spricht daher auch nicht von Polyzythämie in Verbindung mit Herzinsuffizienz.

In meinem Material habe ich keinen Fall von kompensierter Mitralklenose und auch keinen an einem anderen kompensierten Klappenfehler leidenden Patienten gefunden, dessen Erythrozytenzahl die genannten Grenzwerte von Harrop und Wintrobe überschritte. Auch Werte, die höher als die gewöhnlichen Mittelwerte der Erythrozytenzahl, 5.0 und 4.5 Millionen, waren, kamen nur bei zwei Patienten mit kompensiertem Mitralfehler vor.

Diese beiden waren Männer, und der eine von ihnen litt, von seinem Herzfehler abgesehen, an Pneumonie. Sein Hämoglobin war 80 Sahli und seine Erythrozytenzahl 5.22 Millionen. Der andere hatte ausser seinem Herzfehler eine leichte Thyreotoxikose. Dieser Patient war zweimal im Krankenhaus, beide Male überschritt seine Erythrozytenzahl 5.0 Millionen und war das erste Mal 5.13 und das zweite 5.04 Millionen. Die entsprechenden Hämoglobinwerte waren 88 und 90 Sahli. Trotz der etwas erhöhten Erythrozytenzahl können diese Fälle meines Erachtens nicht als solche von Polycythaemia symptomatiea aufgefasst werden.

Das Ergebnis ist ein ganz anderes, wenn wir die Fälle von inkompensiertem Mitralfehler betrachten. Bei zwei von diesen traten leicht, aber deutlich polyzythämische Werte auf, und ausserdem überstieg bei 11 die Zahl der roten Blutkörperchen 5.0 bzw. 4.5 Millionen, ohne jedoch den Grenzwert von Harrop und Wintrobe zu erreichen. Bei den gleichzeitig im Krankenhaus gewesenen Patienten mit einer durch andere Herzfehler hervorgerufenen Herzinsuffizienz konstatierte ich andererseits in zwei Fällen eine deutliche Polycythaemia symptomatiea und in 12 Fällen Werte, die höher waren als die durchschnittliche Erythrozytenzahl. In den beiden ersteren Fällen bestand die Herzkrankheit in Myodegeneratio cordis ohne Klappenfehler, in den 12 letztgenannten Fällen war die Grundkrankheit einmal Aortenklappenfehler und in 11 Fällen wieder Myodegeneratio cordis. Im ganzen gehörten zu meinem Material also vier deutliche Fälle von Polycythaemia symptomatiea im Zusammenhang mit Herzinsuffizienz. Zwei von diesen

hatten einen Mitralfehler. Werte über der mittleren Erythrozytenzahl ohne sicher nachgewiesene Polyzythämie stellte ich wiederum bei insgesamt 23 Herzinsuffizienzpatienten fest, von denen 11 einen Mitralfehler, einer einen Aortenfehler und 11 Myodegeneration cordis ohne Klappenfehler hatten.

Sehen wir uns zuerst die 4 Herzinsuffizienzfälle an, die eine deutliche Polycythaemia symptomatica anwiesen. Zwei Patienten waren Männer und zwei Frauen. Die Männer waren 69 und 33, die Frauen 57 und 43 Jahre alt. Ihre subjektiven Symptome beruhten ganz und gar auf den durch die Herzinsuffizienz ausgelösten Krankheitszeichen, wobei Atemnot, Herzklopfen und Ödeme im Vordergrund standen. Zwei von diesen vier klagten auch über Kopfschmerz, der an sich nicht auf Herzinsuffizienz zurückgeführt werden kann. Der eine dieser zwei hatte etwas erhöhten Blutdruck, aber doch keinmal mehr als 160, bei den meisten Messungen 120—140. Der Blutdruck der anderen war nicht angestiegen. Es dünkt mithin sehr wahrscheinlich, dass die Polyzythämie einen Anteil an dem bei diesen Patienten aufgetretenen Kopfschmerz gehabt hat. Keiner von ihnen hatte Blutungen. Anamnestisch lagen auch keine Daten vor, die man mit etwaigen Thrombosen in Zusammenhang bringen könnte. Über die Menses der Patientinnen liegt in diesen Fällen keine Angabe vor. Auch sonstige möglicherweise innersekretorische Störungen wurden nicht festgestellt.

Der eine der männlichen Patienten war von gewöhnlichem Körperbau, Länge 172 cm, Gewicht 66.3 kg. Als Gewicht ist in diesen wie auch in den anderen Fällen natürlich das Körpergewicht des Patienten nach dem Verschwinden der Insuffizienzsymptome, vor allem der Ödeme angegeben. Der andere Mann war von kräftiger Konstitution und recht beleibt. Seine Länge betrug 162 cm, sein Gewicht 71.6 kg. Der Bau der beiden weiblichen Patienten war gewöhnlich, und beide waren ziemlich mager, das Körpergewicht der einen 51.9 kg, das der anderen 43.4 kg. Ihre Länge ist in den Krankenberichten nicht vermerkt. Die Farbe der Haut und der Schleimhäute war in den verschiedenen Fällen recht verschieden, und es hat den Anschein, als hätte sie einigermaßen von der Menge der roten Blutkörperchen abgehängt. Die Farbe war nämlich bei dem Mann, der die grösste Erythrozytenzahl hatte, ungewöhnlich rot. Bei dem anderen Mann wurde eine starke Zyanose im Gesicht, an den Armen und Beinen konstatiert, während bei den beiden Patientinnen, bei denen die Erythrozytenzahl am kleinsten war, nur eine leichte Zyanose festgestellt wurde. Bei dem älteren Mann trat eine deutliche Arteriosklerose in den peripherischen Blutgefässen auf, bei den anderen nicht. Die Pulsfrequenz schwankte bei drei zwischen 65 und 75, bei einem zwischen 115 und 125 in der Minute. Die letztere hohe Zahl beruhte offenbar auf der schweren Herzinsuffizienz, an der der Patient starb, ohne dass die Herzmedikation einen nennenswerten Einfluss darauf hatte. Sämtliche Patienten bekamen entweder Digitalis oder Strophanthin. Die Milz war in keinem einzigen Fall palpatorisch oder perkussorisch vergrössert.

Tabelle 2.

	Alter	Geschlecht	Hb Sahli	Erythrozy- ten Mill.	Färbe- index	Leukozyten	Lympho- zyten %	Lympho- zyten Zahl
1.	69	♂	103—108	5,640—6,270	0.87—0.91	9,100—23,100	13.0—18.0	1,638—3,003
2.	33	♂	92	6,220	0.74	8,700	21.5	1,871
3.	57	♀	80—95	4,780—5,560	0.83—0.87	4,800		
4.	43	♀	70—95	4,210—5,400	0.83—0.91	6,300—11,150	15.6—29.1	1,659—2,183

## Diagnosen der Fälle:

1 und 2 Myodegeneratio et insufficientia cordis.

3 und 4 Insufficiencia valvulae mitralis. Stenosis ostii atrioventricularis sin. Insufficiencia cordis.

Tabelle 2 veranschaulicht die wichtigsten Befunde bei den Blutuntersuchungen dieser Patienten. Daraus geht hervor, dass die Zahl der roten Blutkörperchen bei allen über die Grenzwerte von Harrop und Wintrobe gestiegen ist. Der Wert des Hämoglobins hat auch ein wenig zugenommen, und zwar ist diese Zunahme proportional der Erhöhung der Erythrozytenzahl, wie aus dem Färbeindex zu erkennen ist, der völlig normal ist, abgesehen von dem einen männlichen Patienten, bei dem jedoch nur eine Blutuntersuchung ausgeführt wurde. Sein Färbeindex ist wenig, aber doch deutlich etwas erniedrigt, 0.74. Die hohen Erythrozyten- und Hämoglobinwerte traten in allen Fällen während der starken Insuffizienz auf, wogegen die kleinen Werte nach der Heilung der Insuffizienz vor der Entlassung der Patienten aus dem Krankenhaus festgestellt wurden. Bei dem einen männlichen Patienten wurde nur eine Blutuntersuchung ausgeführt. Seine Insuffizienz führte trotz der Therapie zum Exitus. Bei dem Fall 1 zeigte sich einmal eine stark erhöhte Leukozytenzahl, 23,100. Dies dürfte jedoch ein auf die eine oder andere Weise fehlerhaftes Ergebnis sein, denn die am folgenden Tag bei ihm ausgeführte Kontrolluntersuchung ergab als Leukozytenzahl nur 9,700. Eine unbedeutende Leukozytose fand sich in diesem Fall jedoch bei allen Bestimmungen. Fall 4 litt ausser an seiner anderen Krankheit an einer nicht genauer ermittelten Infektion. Er hatte Fieber bis 38.6°.

und bei der ersten Blutuntersuchung betrug seine Leukozytenzahl 26,300. Da dieser Wert angeseheinlich auf seiner Infektion beruhte, habe ich ihn nicht in die Tabelle aufgenommen. Bei ihm bestand jedoch auch nach der Beseitigung der Infektion bei den einen Bestimmungen eine leichte Leukozytose, bei den anderen dagegen eine ganz gewöhnliche Zahl der weissen Blutkörperchen. In den Fällen 2 und 3 kam keinmal eine Leukozytose vor. Wie in den Polycythaemia symptomatica-Fällen bei angeborenen Herzfehlern variiert die prozentuale Menge der Lymphozyten auch jetzt erheblich. Dieses Schwanken ist jedoch auch da einigermassen umgekehrt proportional den Variationen in der Gesamtmenge der weissen Blutkörperchen, woraus folgt, dass die absolute Zahl der Lymphozyten fortgesetzt innerhalb der normalen Werte bleibt, abgesehen von der möglicherweise fehlerhaften Bestimmung in Fall 1.

Bei einem Patienten fand sich eine ganz leichte Eosinophilie, 5 %. Jugendzellen der Blutkörperchen kamen bei keinem im Blute vor.

Die Senkungswerte zeigen, dass zu der Leukozytose von Fall 4 die Infektion zum mindesten teilweise beigetragen hat. Seine Blutsenkung betrug nämlich zwischen 12/37 und 46/79 mm. Bei Fall 1 wurde die Senkung nur einmal festgestellt und war da 7/22 mm. Die Senkung von Fall 2 war 0/0 mm, wie im allgemeinen bei der Polycythaemia essentialis. In Fall 3 wurde die Senkungsreaktion nicht bestimmt.

Der Ikterusindex nach Meulengracht wurde nur in Fall 3 bestimmt, und die da gefundenen Werte lagen zwischen 1: 29 und 1: 11, waren also durchgängig erhöht.

Albumin kam bei keinem im Harn vor, so dass keiner eine Nephritis und auch keiner eine Nierenaustauung hatte.

In allen den Fällen, in denen die Herztherapie die Symptome der Herzinsuffizienz beseitigte, verschwand die Polyzythämie ausschliesslich durch diese Behandlung vollkommen, wie aus den kleineren Werten der in Tabelle 2 wiedergegebenen Blutuntersuchungen hervorgeht. Eine unmittelbar auf die Polyzythämie gerichtete Therapie kam nicht zur Anwendung. Zu der Behandlung der Herzinsuffizienz gehörte zwar eine in Fall 1 einmal ausgeführte Venäsektion von 100 ml. Eine so kleine Venäsektion hat jedoch keine Wirkung auf das rote Blutbild. In Fall 4 erfolgte auch einmal eine Venäsektion von 320 ml. Die Insuffizienz der Patientin befand sich da schon im Besserungsstadium, und die Erythrozytenzahl war vor der Venäsektion von 5.4 Millionen auf 4.9 Millio-

nén gesunken, so dass auch in diesem Fall die Behandlung der Herzinsuffizienz an sich deutlich auf die Polyzythämie einwirkte.

In Tabelle 3 stelle ich die Werte des roten Blutbildes aus den 23 Herzinsuffizienzfällen zusammen, deren Erythrozytenzahl die Werte 5.0 Millionen bei Männern und 4.5 Millionen bei Frauen übersteigt, aber unterhalb der Grenzwerte von Harrop und Wintrobe bleibt. Die Fälle 4, 6, 15, 17, 19 und 20 sind auch in dem Material von M. Ch. Ehrström enthalten, desgleichen die beiden Patientinnen von den oben angeführten vier deutlichen Polyzythämiefällen im Zusammenhang mit Herzinsuffizienz.

Aus der Tabelle wird ersichtlich, dass sowohl die Zahl der roten Blutkörperchen als das Hämoglobin im gleichen Verhältnis zugenommen haben, denn ein paar ganz leicht erhöhte Färbeindex abgerechnet, haben alle anderen Patienten einen normalen Färbeindex. Ausser den zwei Fällen, deren Erythrozytenzahl am allerkleinsten war, war die Zahl der roten Blutkörperchen in sämtlichen Fällen, in denen sie sowohl während der Insuffizienz als danach bestimmt wurde, regelmässig niedriger nach der Insuffizienz. Dasselbe gilt von den entsprechenden Hämoglobinwerten. In Fall 22 sind die Zahlen praktisch während und nach der Insuffizienz die gleichen, und in Fall 23 übersteigt die Erythrozytenzahl 4.5 Millionen erst bei der nach der Insuffizienz vorgenommenen Bestimmung.

In Fall 1 erhob sich klinisch auch Verdacht auf Ayerzasche Krankheit, da diese Diagnose aber unsicher war und der Patient eine deutliche Herzinsuffizienz hatte, habe ich ihn im Zusammenhang mit den Herzinsuffizienzen behandelt. In den Fällen 7 und 9 litt der Patient neben der Herzinsuffizienz an Zuckerkrankheit. Zum mindesten in Fall 7 dürfte es sich um eine durch Herzinsuffizienz hervorgerufene Polycythaemia symptomatiea gehandelt haben, da die Polyzythämie nach der Heilung der Herzinsuffizienz verschwand. In Fall 9 kann wohl ausser der Herzinsuffizienz die durch den Diabetes ausgelöste Polyurie zur Erhöhung der Erythrozytenzahl beigetragen haben. Unter diesen Umständen würde hier denn auch eine Pseudopolyzythämie vorliegen. In den Fällen 14, 16 und 21 hatten die Patienten ausser der Herzinsuffizienz ein Lungenemphysem, welches auch Polycythaemia symptomatica verursachen kann, wie ich weiter unten darlegen werde. Die Fälle sind jedoch darum zu denen von Herzinsuffizienz gerechnet worden,

Tabelle 3.

	Geschlecht	Während der Insuffizienz			Nach der Insuffizienz		
		Hb Sahli	Erythro- zyten Mill.	Färbe- index	Hb Sahli	Erythro- zyten Mill.	Färbe- index
1.	O <sub>1</sub>	104	5,940	0.86	90		
2.	O <sub>1</sub>	105	5,720	0.92	86	4,920	0.91
3.	O <sub>1</sub>	93	5,390	0.86	78	4,730	0.91
4.	O <sub>1</sub>	90	5,300	0.85	79	4,520	0.87
5.	O <sub>1</sub>	90	5,260	0.87		4,570	0.86
6.	O <sub>1</sub>	85	5,220	0.82	80	4,950	0.80
7.	O <sub>1</sub>	95	5,210	0.91	83	4,720	0.88
8.	O <sub>1</sub>	95	5,150	0.91			
9.	O <sub>1</sub>	100	5,140	0.98			
10.	O <sub>1</sub>	85	5,140	0.83			
11.	O <sub>1</sub>	90	5,130	0.88			
12.	O <sub>1</sub>	80	5,130	0.78			
13.	O <sub>1</sub>	90	5,090	0.88			
14.	O <sub>1</sub>	90	5,080	0.88			
15.	O <sub>1</sub>	90	5,060	0.88			
16.	O <sub>1</sub>	90	5,030	0.90	80	4,930	0.82
17.	O <sub>1</sub>	85	4,980	0.85	75	4,460	0.83
18.	O <sub>1</sub>	85	4,860	0.87			
19.	O <sub>1</sub>	80	4,780	0.83	80	4,600	0.87
20.	O <sub>1</sub>	75	4,660	0.80	70	4,200	0.83
21.	O <sub>1</sub>	78	4,630	0.85			
22.	O <sub>1</sub>	72	4,540	0.80	75	4,560	0.82
23.	O <sub>1</sub>	68	4,200	0.81	80	4,620	0.87

weil die Herzinsuffizienz hier das Krankheitsbild dermassen beherrschte, dass die Fälle 14 und 16 trotz der Digitalistherapie an der Herzinsuffizienz starben.

*e. Die durch Lungenkrankheiten verursachte Polyeythaemia symptomaticea.*

Von den Lungenkrankheiten können theoretisch alle die, welche die Oxydation des Blutes in den Lungen erschweren, Polyeythaemia symptomaticea verursachen. Die Verhinderung der

Oxydation hinwieder kann entweder von Kreislaufstörungen in den Lungen oder von Erkrankungen des Lungengewebes, besonders der Wand der Alveolen herrühren. Durch Lungenkrankheiten ausgelöste Polyzythämie ist jedoch im allgemeinen nur in Verbindung mit Lungenemphysem und auch da in relativ leichter Form angetroffen worden.

Mein Material bietet zwei Fälle, in denen ein Lungenemphysem mit aller Wahrscheinlichkeit eine deutliche Polyzythämie hervorgerufen hat. Der eine von ihnen ist ein 66jähriger Mann, der ausser dem Lungenemphysem auch eine Herzinsuffizienz hat. In diesem Fall haben wir mithin zwei Faktoren, die beide Polyzythämie verursachen können, das Lungenemphysem und die Herzinsuffizienz. Ich habe diesen Fall darum zu den durch Lungenemphysem ausgelösten Fällen gerechnet, weil die Polyzythämie des Patienten zwar nach der Behandlung der Herzinsuffizienz ein wenig abnahm, aber nicht ganz verschwand, wie es in den oben besprochenen durch Herzinsuffizienz verursachten Polyzythämiefällen geschah. Der andere der zwei Fälle ist eine 62jährige Frau, und auch bei ihr besteht neben dem Lungenemphysem eine Herzinsuffizienz. Die letztere besserte sich während der Therapie etwas, verschwand aber in diesem Fall nicht ganz. Klinisch wurde auch der Verdacht geschöpft, dass die Patientin die Ayerzasche Krankheit oder Pulmonalsklerose habe. Sie starb im Krankenhaus an plötzlichem Herztod während des Heilungsstadiums der Herzinsuffizienz. Bei der Obduktion wurde festgestellt, dass es sich nicht um Pulmonalsklerose handelte, sondern nur um ein starkes Emphysem und eine davon herrührende Hypertrophie vorzugsweise der rechten Herzhälfte sowie um eine Stase in allen inneren Organen. Ich habe diesen Fall zu den Lungenemphysemfällen gezählt, weil das Emphysem hier sowohl im klinischen Krankheitsbild als im Obduktionsbefund dominierte, weil die Herzinsuffizienz deutlich eine Folge des schweren Emphysems war und weil die Polyzythämie der Patientin nicht einmal während der Behandlung zurückging, obwohl die Symptome der Herzinsuffizienz deutlich schwächer wurden.

Das subjektive Symptom beider Patienten bestand hauptsächlich in schwerer Atemnot. Die Patientin hatte früher Ödeme gehabt, aber nicht mehr bei der Aufnahme in das Krankenhaus. Blutungen waren bei beiden nicht vorgekommen, auch lagen keine anamnestischen Daten vor, die Ver-

dacht auf Thrombosen hätten erregen können. Kein Kopfschmerz. Keine Angaben über innersekretorische Störungen.

Der Patient war kräftig gebaut, aber ziemlich mager; Länge 168 cm, Gewicht 59.2 kg. Die Patientin war grazil und mager; Länge 155 cm, Gewicht 45.5 kg. Im Gesicht des Mannes war Zyanose zu konstatieren, und seine Schleimhäute waren rot. Die Patientin hatte starke Zyanose im Gesicht, an den Armen und den sichtbaren Schleimhäuten. Der Brustkorb beider war stark emphysematisch. Beide hatten deutliche Zeichen peripherischer Arteriosklerose. Der Blutdruck des Mannes war 128 bis 118 mm Hg, der der Patientin wurde nur einmal gemessen, wobei er 145/108 mm Hg betrug. Die Pulsfrequenz war wechselnd bei dem Mann 65—75, bei der Frau 75—85 in der Minute. Die Milz des Mannes war weder palpatorisch noch perkussorisch vergrößert, die der Frau war perkussorisch handtellergröss, bei der Obduktion wurde aber festgestellt, dass sie 138 g wog, so dass sie eher klein war, da das Gewicht der Milz gewöhnlich 180—225 g ist.

Bei den Blutuntersuchungen betrug das Hämoglobin des Mannes 108—118 Sahli, die Erythrozytenzahl 7.10—7.16 Millionen, der Färbeindex 0.76—0.82, die Leukozytenzahl 8,400—13,450, das Lymphozytenprozent 22.7—24.6 und die absolute Zahl der Lymphozyten 2,066—3,054. Das Prozent der Eosinophilen bewegte sich zwischen 0.7 und 2.9, das der basophilen zwischen 0 und 0.3, und einmal wurden bei ihm im Blute 1.0 % neutrophile Myelozyten konstatiert. Bei der Frau waren diese Zahlen: Hämoglobin 95—105 Sahli, Erythrozyten 5.51—5.74 Millionen, Färbeindex 0.85—0.95, Leukozyten 5,150—9,200, Lymphozytenprozent 34.0—39.5 und Zahl der Lymphozyten 2,070—3,500. Die Zahl der Eosinophilen belief sich bei ihr auf 2.0 bis 10.0 %, Basophile fanden sich nicht im Blute und ebensowenig Jugendformen.

Bei dem Mann ist die Senkungsreaktion nicht bestimmt worden. Bei der Frau war sie 4 mal 0/0 und einmal 1/2 mm. Der Ikterusindex nach Meulengraecht wurde nur bei der Frau bestimmt, und er war 1:40.

Bei dem Mann enthielt der Urin kein Eiweiss, bei der Frau ein wenig, die Albuminprobe opaleszierte, im Sediment nur Leukozyten. Der Reststickstoff der Frau betrug 71 mg %.

Bei dem männlichen Patienten wurde kurz vor seiner Entlassung aus dem Krankenhaus eine Venäsektion von 375 ml ausgeführt, der Patientin wurde keine Behandlung gegeben, durch die versucht worden wäre, auf ihre Polyzzythämie einzuwirken.

Ausser in diesen Fällen stieg bei neun Lungenemphysempatienten die Zahl der roten Blutkörperchen über die durchschnittliche



Tabelle 4.

	Alter	Ge- schlecht	Hb Sahli	Erythro- zyten Mill.	Färbe- index	Leuko- zyten
1.	47	♂	110	5,960	0.93	7,300
2.	56	♂	100	5,700	0.87	6,100
3.	44	♂	94	5,450	0.85	8,000
4.	75	♂	95	5,100	0.93	4,100
5.	61	♂	90	5,080	0.90	7,800
6.	57	♂	75	5,010	0.75	14,600
7.	55	♀	85	4,780	0.90	6,700
8.	33	♀	90	4,730	0.95	6,300
9.	41	♀	80	4,530	0.88	8,300

Erythrozytenzahl gesunder Personen, 5 Millionen bzw. 4.5 Millionen. Von diesen waren 6 Männer und 3 Frauen. Bei allen Patientinnen war das Emphysem hinwieder eine Folge von Lungenasthma. Von den männlichen Patienten hatte dagegen keiner Asthma. Die Blutbilder dieser Fälle sind in Tabelle 4 wiedergegeben.

Aus der Tabelle geht hervor, dass das Alter der männlichen Patienten zwischen 44 und 61, bei den weiblichen zwischen 33 und 55 Jahren schwankte. Das niedrigere Alter der Frauen erklärt sich natürlich daraus, dass ihr Emphysem durch das Asthma verursacht war. Das Hämoglobin betrug wechselnd 75—110 Sahli, die Zahl der roten Blutkörperchen 4.53—5.96 Millionen und der Färbeindex 0.75—0.95. Fall 4 hatte eine leichte Leukopenie, 4,100 Leukozyten und Fall 6 eine deutliche Leukozytose, 14,600, die jedoch deutlich auf der gleichzeitigen Pneumonie des Patienten beruhte. Bei den anderen war die Zahl der weissen Blutkörperchen die gewöhnliche, zwischen 6,100 und 8,300 wechselnde.

*d. Die durch Ayerzasche Krankheit verursachte Polycythaemia symptomatica.*

Ayerza beschrieb erstmals im Jahre 1901 die unter seinem Namen bekannte Krankheit. In dem Krankheitsbild dominiert als zentrales Symptom die Pulmonalsklerose, d. h. insbesondere die

in die Pulmonalarterie lokalisierte Arteriosklerose. Rogers stellte zuerst fest, dass die Pulmonalsklerose sehr oft von Lues herrührt. Auch kongenitale Verengerungen der Lungenschlagader sind nach Harrop und Wintrobe angetroffen worden. Mit der Krankheit verknüpft sich in der Regel ein deutliches Lungenemphysem, und diese zentralen Symptome führen alsbald, indem sie den freien Zutritt des Blutes zu den Lungen verhindern, zu einer Hypertrophie der rechten Herzhälfte und rufen auch eine Polyzythämie hervor, die in diesen Fällen recht intensiv sein kann. Nach Morse würde dieses Krankheitsbild durch Sklerose der feinsten Verästelungen der Lungenschlagader und nicht durch Arteriosklerose der Pulmonalarterie selbst und ihrer grössten Äste entstehen. Die Krankheit ist überall relativ selten, kommt aber verhältnismässig öfter in den Tropen vor. Im allgemeinen ist es recht schwer, sie auf Grund klinischer Symptome zu diagnostizieren.

In meinem Material findet sich eine Patientin mit Ayerzascher Krankheit, eine 44jährige Näherin. Sie hat an den gewöhnlichen Kinderkrankheiten sowie als Mädchen an Lungenentzündung und Rachitis gelitten. Morbi venerei negantur. Nach dem als Kind durchgemachten Scharlach ist sie von Atemnot belästigt worden, und ihre Lippen sind seitdem bläulich gewesen. Sie hat niemals schwerere Arbeit auszuführen vermocht. Die Menses begannen bei ihr mit 17 Jahren, Dauer 3—4 Tage, Menge wie gewöhnlich. Im vorigen Winter manchmal 6-8wöchige Intervalle, sonst regelmässig. Weder Kopfschmerz noch Blutungen und keine anamnестischen Angaben über Thrombosen. Im Sommer 1943 schwellen die Beine an, und die Atemnot verschlimmerte sich. Wurde in einem Provinzialkrankenhaus behandelt, und während dieser Therapie gingen die Ödeme bedeutend zurück.

Die Patientin ist von zartem Bau; Länge 156 cm, Gewicht 45.2 kg. Keine Ödeme. Gesicht, besonders Ohren und Lippen, bläulichrot. Nervensystem o. B. Die Grenzen der Herzdämpfung befinden sich links im fünften Zwischenrippenraum in der Medioklavikularlinie, im zweiten Zwischenrippenraum 1 Fingerbreit vom Rand des Brustbeines nach links und rechts im zweiten Zwischenrippenraum sowie im vierten Zwischenrippenraum 1 Fingerbreit vom Rand des Brustbeines nach rechts. Die Herztöne sind mässig kräftig, ihr Schall ist etwas herabgesetzt, ein deutliches systolisches Geräusch ist an der Spitze sowie der Basis zu hören, keine Akzente. Keine Zeichen peripherischer Arteriosklerose. Blutdruck 125 mm Hg. Pulsfrequenz zwischen 65 und 75/Min. Der Thorax ist bei der VI—VII Rippe zusammengeschnürt. Die Lungen-Lebergrenze liegt bei der VI Rippe. In den hinteren unteren Teilen beider Lungen hört man sowohl trockenes pfeifendes als feuchtes weiches Rasseln. Die Leber erstreckt

sich 1 Fingerbreit unter den rechten Rippenbogen. Milz nicht nachweisbar vergrössert. Alb. —. Röntgenologisch wurde ein vorzugsweise nach rechts, aber auch ein wenig nach links vergrössertes Herz, ein stark pulsierender Pulmonalbogen, ein dilatierter Conus pulmonalis und in den Lungen sowohl eine vermehrte Lungenzeichnung als eine erhöhte interstitielle Fibrose konstatiert. Elektrokardiographisch deutliche Zeichen von Myodegeneration. Grundumsatz + 18 %. Blutkalzium 10.8 mg %. WR +, Kahn +. Senkungsreaktion 0/1 mm.

Bei den Blutuntersuchungen betrug das Hämoglobin wechselnd 90—112 Sahli, die Zahl der roten Blutkörperchen 5.01—6.24 Millionen, der Färbeindex 0.86—0.90 und die Leukozytenzahl 4,800—8,800. Eine Differenzierung der Leukozyten wurde nur einmal vorgenommen und ergab 26.0 % Lymphozyten, während die Gesamtzahl der Lymphozyten 1,352 war. Eosinophile waren 3.0 % und Basophile 0 vorhanden. Die kleinsten Hämoglobin- und Erythrozytenwerte wurden 10 Tage vor dem Exitus festgestellt, nachdem die Patientin an Bronchopneumonie erinnerndes Fieber mit Lungenveränderungen gehabt hatte.

Die Senkungsreaktion war 0/1 mm, stieg aber ante exitum, während die Menge des Hämoglobins und die Erythrozytenzahl zugleich sanken, auf 30 mm in der ersten Stunde an.

Auf die Polyzythämie gerichtete Therapie wurde der Patientin nicht gegeben.

Bei der Obduktion konnten reichlich arteriosklerotische Veränderungen in der Lungenschlagader selbst und ihren grösseren Ästen, also typische, der Ayerzaschen Krankheit eigentümliche Veränderungen nachgewiesen werden. Ausserdem wurden eine starke Hypertrophie der rechten Herzhälfte und alte kleine tuberkulöse Herde in den Lungen gefunden.

### 3. Die *Polycythaemia symptomatrica* bei Personen, die in hohen Gebirgsgegenden leben.

Auf hohen Bergen geht der Druck des Sauerstoffs so weit herab, dass der Sauerstoff in den Lungen nicht in erforderlicher Menge an das Hämoglobin gebunden wird und der Organismus infolgedessen an Sauerstoffmangel leidet. Zur Kompensation des Sauerstoffmangels löst der Organismus solcher Personen eine symptomatische Polyzythämie aus. Dies beobachtete erstmals Viault 1890

bei seinen Blutuntersuchungen unter den Bewohnern der Anden. Bert hatte schon 1878 die Vermutung ausgesprochen, dass der Organismus wahrscheinlich den Sauerstoffmangel in derartigen Fällen durch Steigerung der Hämoglobinmenge und der Erythrozytenzahl kompensiere. Später wurde nachgewiesen, dass diese Veränderungen reversibel sind und dass, wenn eine früher auf hohen Bergen wohnende Person dauernd in ein Tal übersiedelt, ihre Blutwerte allmählich auf dasselbe Niveau zurückkehren wie im allgemeinen bei den im Tale wohnenden Menschen.

Mein Material enthält keinen Fall dieser Art.

#### 4. Die durch Vergiftungen verursachte *Polycythaemia symptomtica*.

Nach Harrop und Wintrobe rufen mehrere Gifte verschiedener Art, besonders in kleinen Dosen genossen, Polyzythämie hervor. Zu diesen gehören nach ihnen manche Metalle, worunter namentlich bei dem Kobalt eine recht starke die Erythrozytenzahl erhöhende Wirkung nachgewiesen worden ist, Schellack, manche Anilinderivate und die Gifte, die Sulfhämoglobin und Methämoglobin erzeugen.

In meinem Material findet sich kein durch Gifte hervorgerufener Fall von *Polycythaemia symptomtica*.

### Besprechung der Ergebnisse.

#### 1. Die durch angeborene Herzfehler verursachte *Polycythaemia symptomtica*.

Die Zahl der Fälle ist in dem Material vier. Die Diagnose gründet sich in allen ausschliesslich auf das klinische Krankheitsbild. Von den Fällen ist einer eine bis zu relativ hohem Alter, zu ihrem 23. Lebensjahr gelangte, an Pulmonalstenose leidende Frau, einer ein an Ductus Botalli apertus leidender Mann und zwei mit einem Ventrikelseptumdefekt behaftete Patienten, ein Mann und eine Frau. Die beiden Geschlechter sind also durch je zwei Fälle vertreten.

Die Beschwerden, über die alle klagen, lassen sich leicht auf ihren Herzfehler zurückführen. Direkt durch die Polyzythämie verursachte Beschwerden waren dagegen anamnestisch nicht fest-

zustellen. Die an dem Ventrikelseptumdefekt leidende Frau wurde wegen Blutspucken in das Krankenhaus aufgenommen. Weder die klinische noch die röntgenologische Untersuchung erklärte genau, worauf dieses Blutspucken hernhte. Da das Blut jedoch wenigstens während des Anstaltsaufenthalts der Patientin in Form von Blutstreifen in den Auswürfen antrat und nicht besonders dunkel war, dürfte es sich kaum um einen als Komplikation des Herzfehlers hinzugekommenen Lungeninfarkt gehandelt haben. Sehr wahrscheinlich ist, dass es von kleinen, in den Lungen lokalisierten Thromben herrührte, denn bei der Polyzythämie kommen ja sehr oft wegen der grossen Viskosität des Blutes Thromben in verschiedenen Teilen des Körpers vor. In der Anamnese des Mannes mit Ductus Botalli apertus war auch angegeben, dass er sein Sprachvermögen zufällig für einige Tage verloren hatte. Auch hieran dürften im Gehirn lokalisierte Thromben schuld gewesen sein.

Blutungen kamen in keinem Fall vor, ebensowenig der bei Polycythaemia essentialis so gewöhnliche Kopfschmerz. Durch innersekretorische Störungen bedingt war vermutlich das Ausbleiben der Meneses bei der an Pulmonalstenose leidenden Patientin 5 Monate vor der Ankunft in dem Krankenhaus. Innersekretorische Störungen sind bekanntlich bei Polyzythämie, insbesondere bei Polycythaemia essentialis, sehr häufig.

Aus der Konstitution der Patienten lassen sich in einem so kleinen Material keine Schlüsse ziehen. Alle wiesen in den vorstehenden Körperteilen eine starke Zyanose auf. Rote Hautfarbe wurde dagegen bei keinem festgestellt. Keiner hatte auch arteriosklerotische Veränderungen in den peripherischen Blutgefässen. Die Pulsfrequenz war verhältnismässig gering, meist zwischen 55 und 65/Min. wechselnd, aber zu diesem langsamen Puls kann auch die diesen Patienten gegebene Digitalistherapie beigetragen haben. Zwei Patienten hatten leicht erhöhten Blutdruck. Die Milz war bei keinem einzigen vergrössert.

Alle hatten eine deutlich ausgeprägte Polyzythämie, die Zahl der roten Blutkörperchen erhob sich auch bei dem Patienten mit den niedrigsten Blutwerten auf 6.62 Millionen, und dazu war dieser Patient eine Frau. Die grösste Erythrozytenzahl, 9.9 Millionen, gehört derselben Grössenklasse an wie die höchsten im Zusammenhang mit kongenitalen Herzfehlern beobachteten Erythrozyten-

zahlen. Der Färbeindex war im allgemeinen normal, so dass die Zahl der roten Blutkörperchen und der Hämoglobingehalt im gleichen Verhältnis angestiegen waren. Bei einem Patienten trat eine deutliche Leukozytose auf, wofür nur die Polyzythämie verantwortlich gemacht werden konnte. Die absolute Menge der Lymphozyten war im grossen und ganzen normal, obwohl eine geringe Abweichung von den Normalbildern sowohl nach oben als nach unten vorkam. Die Senkungsreaktion sämtlicher Patienten war typischerweise sehr niedrig. Der Wert der ersten Stunde lag zwischen 0 und  $\frac{1}{2}$  mm. Nur bei einem Patienten wurde der Ikterusindex untersucht, und dieser war normal.

An die Polyzythämie schliesst sich oft Nephritis an. Bei zwei Patienten fand sich Eiweiss im Harn, aber bei dem einen beruhte es offenbar auf einer durch Herzinsuffizienz verursachten Nierenumstauung, bei dem anderen lag dagegen eine deutliche Nephritis vor.

Auf die Polyzythämie gerichtete Therapie wäre bei der durch angeborene Herzfehler hervorgerufenen Polycythaemia symptomata sinnlos, da die Polyzythämie in diesen Fällen, wie überhaupt die Polycythaemia symptomata, ein Abwehrmittel des Organismus gegen Sauerstoffmangel ist. Nur in den Fällen, in denen sich die Polyzythämie bis zu dem Stadium entwickelt hat, dass der Organismus unmittelbar Schaden von ihr hat, kann auf die Polyzythämie gerichtete Behandlung am Platze sein.

Aus meinen durch erworbene Herzfehler verursachten Polycythaemia symptomata-Fällen ging hervor, dass die Herzinsuffizienz den Sauerstoffmangel recht beträchtlich erhöht und schon an sich Polyzythämie hervorruft. Eine effektive Behandlung der Herzinsuffizienz ist daher ausserordentlich wichtig gerade in Verbindung mit angeborenen Herzfehlern, da die Herzinsuffizienz in diesen Fällen ausser den anderen von ihr herrührenden Schäden auch die Polyzythämie steigert. Auch eine leichte Herzinsuffizienz bei kongenitalen Herzfehlern ist darum meines Erachtens soweit möglich bis zu vollständiger Kompensation zu behandeln.

Da die Herzinsuffizienz die Polyzythämie steigert, ist leicht zu begreifen, dass man bei angeborenen Herzfehlern, wo der Herzfehler schon an sich Polyzythämie verursacht, während der Insuffizienzsymptome im allgemeinen die höchsten Polycythaemia symptomata-Werte antrifft.

## 2. Die durch erworbene Herzfehler ausgelöste *Polycythaemia symptomatrica*.

Mein Material enthält nur zwei kompensierte Mitralfehler, in denen die Zahl der roten Blutkörperchen 5 Millionen bei Männern und 4.5 Millionen bei Frauen überschreitet, und es gehört zu ihm kein Fall, in dem die Erythrozytenzahl über die Grenzwerte von Harrop und Wintrobe hinausginge. Es bietet auch keine anderen kompensierten Klappenfehler, bei denen die Zahl der roten Blutkörperchen erhöht wäre.

Harrop und Wintrobe unterscheiden in ihren Darlegungen über die Polyzythämie bei Mitralkstenose in keiner Weise die kompensierten von den inkompensierten Fällen. Mein Material zeigt meiner Ansicht nach recht deutlich, dass die Erythrozytenzahl zum mindesten in Finnland äusserst selten, wenn je, bei den kompensierten Mitralfehlern oder anderen kompensierten Klappenfehlern auf polyzythämische Werte erhöht ist und dass auch kleine Zunahmen der roten Blutkörperchen recht selten sind.

In Verbindung mit Herzinsuffizienz fand sich *Polycythaemia symptomatrica* in meinem Material dagegen in vier Fällen, und in 23 Fällen lagen wenigstens leicht erhöhte Erythrozytenwerte vor. Unter diesen hatten zwei typische *Polycythaemia symptomatrica*-Fälle und 11 von denen, deren Erythrozytenzahl nur leicht erhöht war, als Grundleiden einen Mitralfehler. Bei den beiden anderen Polyzythämiefällen bestand die Grundkrankheit in Myodegeneratio cordis, und bei den übrigen 12 in der Gruppe der leicht erhöhten Erythrozytenwerte war sie bei einem ein Aortenfehler und bei 11 Myodegeneratio cordis. Praktisch gesehen, hatte also jeder zweite Fall als Grundleiden Myodegeneratio cordis und jeder zweite Mitralkstenose oder kombinierte Mitralkstenose und -insuffizienz. Da nun die Myodegeneratio cordis bekanntlich eine viel häufigere Krankheit als der Mitralfehler ist, dürfte man auf Grund meines Materials behaupten können, dass im Zusammenhang mit einem inkompensierten Mitralfehler relativ öfter *Polycythaemia symptomatrica* vorkommt als in Verbindung mit inkompensierter Myodegeneratio cordis.

Von den vier Patienten, die eine deutliche *Polycythaemia symptomatrica* in Verbindung mit Herzinsuffizienz hatten, waren zwei Männer und zwei Frauen. Die Grundkrankheit war bei den beiden

Männern Myodegeneratio cordis, bei den beiden Frauen ein Mitralfehler. Ihre subjektiven Beschwerden können, abgesehen von dem bei zweien aufgetretenen Kopfschmerz, auf die Herzinsuffizienz zurückgeführt werden. Da nur bei dem einen dieser zwei eine leichte Hypertonie, auch bei ihm jedoch gelegentlich keiner Messung über 160 mm Hg, vorlag, dürfte dieser Kopfschmerz ein direktes Symptom der Polyzythämie gewesen sein, denn Kopfschmerz ist ja bei Polycythaemia essentialis ein sehr gewöhnliches Krankheitszeichen. Blutungen hatte keiner der Patienten, ebensowenig Thrombosen. Innersekretorische Störungen wurden bei keinem festgestellt.

Der eine der männlichen Patienten war von gewöhnlichem Bau, der andere kräftig und zugleich korpulent. Die beiden Patientinnen zeigten gewöhnliche Konstitution und waren, was ihren Ernährungszustand betrifft, mager. Die Farbe der Haut war, wie es bei Polycythaemia essentialis die Regel ist, bei dem Mann mit der höchsten Erythrozytenzahl röter als gewöhnlich, bei den anderen trat in der Haut und den sichtbaren Schleimhäuten eine schwächere oder stärkere zyanotisch wirkende Färbung auf. Der ältere, 69-jährige Mann hatte in den peripherischen Blutgefäßen eine deutliche Arteriosklerose, die anderen nicht. Die Pulsfrequenz war gewöhnlich, ausser bei einem Patienten, bei dem sie 115—125/Min. betrug. Dies beruhte augenscheinlich auf der schweren Herzinsuffizienz, die bald zum Exitus des Patienten führte. Die Milz war bei keinem vergrößert.

Bei den Blutuntersuchungen war zu konstatieren, dass in den drei Fällen, in denen die Zahl der roten Blutkörperchen sowohl während der Insuffizienz als nach ihrem Verschwinden bestimmt werden konnte, die anfangs deutlich polyzythämischen Werte in zwei Fällen auf ganz normale und auch im dritten unter die Grenzwerte von Harrop und Wintrobe herabgingen. Die Erythrozytenzahl war jetzt bei allen bedeutend kleiner als in den bei angeborenen Herzfehlern aufgetretenen Polyzythämiefällen, wo der höchste Wert 9.9 Millionen betrug, während er jetzt nur 6.27 Millionen war. Das Hämoglobin hatte im allgemeinen in demselben Verhältnis wie die Zahl der roten Blutkörperchen zugenommen, so dass der Färbeindex normal blieb. In zwei Fällen trat eine deutliche Leukozytose auf, da aber der eine von ihnen auch eine Infektion hatte, lässt sich nicht entscheiden, ob seine Leukozytose ganz auf dieser



Infektion beruhte oder ob vielleicht auch die Polyzythämie einen Anteil daran hatte. In dem anderen Fall ist die Leukozytose dagegen deutlich als ein Symptom der Polyzythämie zu betrachten. Die absolute Zahl der Lymphozyten blieb praktisch normal. Eine leichte Eosinophilie, 5 %, kam bei einem Patienten vor. Jugendformen der Blutkörperchen hatte keiner im Blute.

Die Senkungsreaktion war in einem Fall 0/0 mm, in einem zweiten 7/22 mm, und bei dem gleichzeitig an einer Infektion leidenden Patienten war sie abwechselnd bei verschiedenen Bestimmungen 12/37 bis 46/79 mm. Bei dem vierten Patienten wurde die Reaktion keinmal festgestellt. Da die Erhöhung der Erythrozytenzahl in diesen Fällen geringer als bei Polycythaemia essentialis und auch geringer als in den Polycythaemia-symptomatica-Fällen in Verbindung mit angeborenen Herzfehlern war, kann die Senkungsreaktion mithin auch ziemlich hoch ansteigen, falls eine andere Krankheit dazu Veranlassung gibt.

Die durch Herzinsuffizienz hervorgerufene Polyzythämie ist keine Pseudopolyzythämie, obwohl sie von Natur nur momentan ist und nach der Heilung der Herzinsuffizienz verschwindet, denn M. Ch. Ehrström hat deutlich gezeigt, dass während der Herzinsuffizienz eine Neubildung von Blutkörperchen in reichlicherem Masse als gewöhnlich stattfindet; hieraus aber ergibt sich, dass die Zahl der Retikulozyten während der Insuffizienz wirklich auf so hohe Werte anwächst, dass diese Zunahme nicht von einer eventuellen durch Flüssigkeitsverlust verursachten Konzentration des Blutes hergerührt haben kann. Nach dem Verschwinden der Insuffizienz sinkt die Zahl der roten Blutkörperchen wieder infolge der dann eintretenden Hämolyse, wie M. Ch. Ehrström in seiner Untersuchung nachgewiesen hat. Aus diesem Grunde gibt der Meulengrachtsche Versuch in diesen Fällen oft erhöhte Werte. Er ist nur in einem meiner Fälle ausgeführt worden, und das Ergebnis war da 1:29 bis 1:11, also während der ganzen Zeit deutlich erhöht.

Eine solche durch Herzinsuffizienz verursachte leichte Polyzythämie dürfte kaum an sich Nierenschädigungen hervorrufen. Bei keinem meiner Patienten fand sich denn auch Eiweiss im Harn, weshalb also auch keine Nierenstauung vorhanden war.

Eine unmittelbar auf die Polyzythämie gerichtete Therapie ist in meinen Fällen nicht angewandt worden, und sie ist auch nicht notwendig gewesen, denn das Blutbild wurde durch aus-

schliessliche Behandlung der Herzinsuffizienz normal. Diese Behandlung umfasste zwar in einem Fall eine einmal ausgeführte Venäsektion von 100 ml und in einem anderen Fall eine solche von 320 ml. So kleine einmalige Venäsektionen spielen jedoch, wie die Erfahrungen bei der Behandlung der Polycythaemia essentialis gezeigt haben, in der fraglichen Beziehung keine nennenswerte Rolle, und sie haben auch nicht wesentlich auf die Blutbilder der von mir behandelten Patienten eingewirkt.

Dasselbe Absinken der Erythrozytenzahlen auf normale Werte nach der Heilung der Herzinsuffizienz wird auch aus den Fällen ersichtlich, in denen die Zahl der roten Blutkörperchen während der Insuffizienz zwar grösser als gewöhnlich war, aber die Grenzwerte von Harrop und Wintrobe nicht überschieg. Nur bei zwei Patientinnen, deren Erythrozytenzahlen die kleinsten in der ganzen Gruppe, nämlich 4.62 und 4.54 Millionen, waren, gingen die Werte der roten Blutkörperchen nicht nach dem Verschwinden der Insuffizienz herab. Man muss wohl annehmen, dass die Herzinsuffizienz in diesen Fällen keinen Anteil an den verhältnismässig hohen Blutwerten der Patientinnen gehabt hat.

### 3. Die durch Lungenemphysem verursachte Polycythaemia symptomatica.

Ein Lungenemphysem ruft Polycythaemia symptomatica offenbar erst hervor, wenn es sich bis zu einem schweren Stadium entwickelt hat. Dabei hat es im allgemeinen auch eine Hypertrophie der rechten Herzhälfte und eine beginnende Herzinsuffizienz ausgelöst. In den mit Lungenemphysem einhergehenden Fällen von Polycythaemia symptomatica sind daher gewöhnlich zwei Polyzythämie verursachende Faktoren vorhanden: das Lungenemphysem und die Herzinsuffizienz. In der Regel ist es sehr schwer, oft sogar unmöglich, zu entscheiden, welcher von beiden die Hauptrolle bei der Entstehung der Polyzythämie spielt. In meiner Arbeit habe ich das Lungenemphysem nur in dem Fall als den Urheber der Polyzythämie betrachtet, dass die Polyzythämie des Patienten nicht verschwunden ist, obwohl die gleichzeitig vorhandene Herzinsuffizienz behandelt und das Herz kompensiert worden ist. Nur in diesen Fällen kann man meiner Ansicht nach mit Sicherheit behaupten, dass die Polyzythämie auf der Grund-

lage des Lungenemphysems entstanden ist, wenn sich zu diesem auch eine Herzinsuffizienz hinzugesellt hat.

Soleher Fälle finden sich in meinem Material zwei. Keimnal hat das Lungenemphysem eine deutliche Polyzythämie, wenn sich daran keine Herzinsuffizienz angeschlossen hat, wohl aber mitunter höhere Erythrozytenzahlen als gewöhnlich hervorgerufen.

Die beiden deutlichen durch Lungenemphysem hervorgerufenen Fälle von Polyeythaemia symptomatiea waren über 60 Jahre alt, der eine ein Mann, der andere eine Frau. In dem Krankheitsbild dominierte bei beiden eine schwere Atemnot. Weder Blutungen noch Thrombosen und auch weder Kopfsehmerz noch innersekretorische Störungen.

Beide zeigten eine starke Zyanose, ein weit fortgeschrittenes Emphysem und deutliche arteriosklerotische Veränderungen in den peripherischen Blutgefässen. Der Blutdruck war nicht nennenswert erhöht, bei dem einen war er 145 mm Hg, bei dem anderen ganz normal. Die Pulsfrequenz war bei beiden gewöhnlich. Die Milz der Frau war perkussorisch vergrössert, aber bei der Obduktion wurde ihr Gewicht zu nur 138 g festgestellt, weshalb der perkussorische Befund offenbar fehlerhaft gewesen war.

Die Zahl der roten Blutkörperchen war bei beiden mässig vermehrt. Die Zunahme des Hämoglobins war proportional der Erhöhung der Erythrozytenzahl, so dass der Färbeindex normal blieb. Der Mann hatte bei allen Blutuntersuchungen eine leichte, aber deutliche Leukozytose, und die Leukozytenzahl der Frau stieg einmal auf 9,200. Die absolute Zahl der Lymphozyten war bei beiden etwas erhöht, aber diese Erhöhung war so gering, dass die in der Gesamtzahl der Leukozyten festgestellte Zunahme nicht ausschliesslich darauf beruhen kann, sondern auch die Zahl der Granulozyten war offenbar vermehrt. Bei dem Mann wurden im Blute einmal neutrophile Myelozyten konstatiert, und die Frau hatte bei den meisten Untersuchungen eine Eosinophilie, einmal sogar bis 10 %. Bei dem Mann ist die Senkungsreaktion nicht bestimmt worden, bei der Frau war sie 0/0 mm. Der bei der Frau ausgeführte Meulengrachtsche Versuch war deutlich erhöht, 1: 40. Sie hatte überdies ein wenig Eiweiss im Harn und erhöhten Reststickstoff, 71 mg %.

Da wir die Grundkrankheit, das Lungenemphysem, nicht nennenswert zu beeinflussen vermögen, ist eine auf die Polyzythä-

nie gerichtete Therapie auch in diesen Fällen unangebracht, wenn die Polyzythämie an sich den Patienten keine weiteren Beschwerden verursacht. Demgemäss ist den Patienten meines Materials keine eigentliche auf die Polyzythämie gerichtete Behandlung gegeben worden. Bei dem männlichen Patienten wurde zwar einmal eine Venäsektion von 375 ml gemacht, aber, wie schon erwähnt, ist die Wirkung einer mittelgrossen Venäsektion auf die Polyzythämie sehr gering. Sie war denn auch in diesem Fall augenscheinlich wegen der Herzinsuffizienz des Patienten ausgeführt worden.

Neun Lungenemphysempatienten hatten in meinem Material ausserdem eine leicht erhöhte Erythrozytenzahl. Von diesen waren drei Frauen, bei denen das Lungenemphysem durch Asthma verursacht war. Bedenkt man, dass das Lungenemphysem bei ihnen eine Folge des Asthmas war, so erhält ihr recht niedriges Alter, 33—55 Jahre, seine Erklärung. Die sechs männlichen Patienten meines Materials hatten dagegen kein Asthma. Doch war auch ihr Alter recht niedrig, 44—61 Jahre.

Wie ich früher konstatiert habe (Hirvonen 1941), schliesst sich an das Ulkus verhältnismässig oft ein Lungenemphysem an. Andererseits ist allgemein bekannt, dass bei Ulkus häufig hohe Erythrozytenzahlen angetroffen werden. So wurden 1939—1943 in der I. medizinischen Klinik sechs Ulkuspacienten behandelt, bei denen die Zahl der roten Blutkörperchen von 5.01 bis 5.15 Millionen variierte. Im Hinblick auf die Häufigkeit des Lungenemphysems bei Ulkus ist es möglich, dass die im Zusammenhang mit Ulkus vorkommenden hohen Erythrozytenzahlen teilweise auch auf einem gleichzeitigen Lungenemphysem beruhen könnten. Andererseits hat man sich ja gedacht, dass die Absonderung von intrinsic factor bei Ulkus vermehrt und dass die hohen Erythrozytenwerte durch diese Zunahme des intrinsic factor bedingt seien.

#### 4. Die durch die Ayerzasche Krankheit ausgelöste Polycythaemia symptomatrica.

Da sich die Pulmonalsklerose bei der Ayerzaschen Krankheit so stark entwickeln kann, dass der Zutritt des Blutes zu den Lungen sich schwerer als gewöhnlich gestaltet, sind bei dieser Krankheit recht hohe Erythrozytenzahlen beobachtet worden.

Mein Material enthält einen durch die Ayerzasche Krankheit

verursachten Fall von Polycythaemia symptomtica. Dieser ist eine 44jährige Frau. Die Ätiologie der Ayerzaschen Krankheit besteht in diesem Fall in der gewöhnlichsten Ursache der Krankheit, nämlich in Lues. Sämtliche serologische Reaktionen gegenüber Lues sind bei der Patientin positiv. Da sie laut Mitteilung seit Scharlach in der Kindheit Atemnot gehabt hatte und da sie nichts von einer Luesinfektion weiss oder wenigstens keine solche zugibt, dürfte es sich um kongenitale Lues handeln. Die Diagnose Pulmonalsklerose wurde bei der Obduktion sichergestellt, und auch da wurde kein Klappenfehler konstatiert, der möglicherweise zur Erklärung der von Kindheit an bestehenden Atemnot hätte dienen können. Die arteriosklerotischen Veränderungen traten in diesem Fall deutlich in der Pulmonalarterie selbst und ihren grössten Ästen auf, nicht in den feinen Verzweigungen der Lungenschlagader, wie Morse behauptet hat.

Das Krankheitsbild der Patientin wurde von der Atemnot beherrscht. Sie hatte keine Blutungen noch Thrombosen oder Kopfschmerz. Vielleicht beruhte es auf innersekretorischen Störungen, dass die Menses vor einem Jahr nur mit 6—8wöchigen Intervallen auftraten.

Von Konstitution war die Patientin grazil. Die vorstehenden Teile des Körpers zeigten Zyanose, keine Arteriosklerose in den peripherischen Blutgefässen. Blutdruck gewöhnlich, ebenso die Pulsfrequenz. Die Milz war nicht vergrössert, keine Zeichen von Nierenkrankheiten. Der Grundumsatz war leicht erhöht, + 18 %. Die Zahl der roten Blutkörperchen war leicht, aber doch ganz deutlich vermehrt, ebenso das Hämoglobin, und der Färbeindex war normal. Leukozytose war nicht festzustellen. Im Blute wurden keine Jugendformen der Blutkörperchen konstatiert. Die Patientin hatte keine Eosinophilie. Das Blutkalzium war normal.

Auf die Polyzythämie gerichtete Therapie ist auch bei dieser Krankheit ohne direkt von der Polyzythämie herrührende Beschwerden nicht angezeigt, da wir nicht auf das Grundleiden einwirken können. Antiluetische Behandlung ist, da es sich um Lues handelt, naturgemäss am Platze, aber es ist recht fraglich, ob die sklerotischen Veränderungen sogar durch antiluetische Therapie auch nur teilweise aus den Lungenarterien verschwinden. Jedenfalls habe ich in der Literatur keine Angaben darüber gefunden. Mein Fall bekam antiluetische Behandlung, aber keine direkt auf die Polyzythämie gerichtete Therapie.

### Zusammenfassung.

Die Ergebnisse gründen sich auf Beobachtungen an 11 deutlichen Polycythaemia symptomatica-Fällen und an 34 Patienten, bei denen die Zahl der roten Blutkörperchen infolge einer anderen Krankheit bei den Männern über 5 Millionen und bei den Frauen über 4.5 Millionen gestiegen war, ohne jedoch deutlich polyzythämische Werte zu erreichen. Als deutliche Polyzythämiefälle habe ich diejenigen gerechnet, in denen die Erythrozytenzahl bei den Männern 6.2 Millionen und bei den Frauen 5.4 Millionen überschreitet. Die Polycythaemia symptomatica war in vier Fällen durch einen angeborenen Herzfehler, in vier Fällen durch einen inkompenzierten erworbenen Herzfehler, in zwei Fällen durch Lungenemphysem und einmal durch die Ayerzasehe Krankheit verursacht worden. Die leicht erhöhte Erythrozytenzahl beruhte wiederum 2 mal auf einem kompensierten erworbenen Mitralfehler, 23 mal auf einem inkompenzierten erworbenen Herzfehler, wobei dieser in 11 Fällen ein Mitralfehler, einmal ein Aortenfehler und 11 mal Myodegeneratio cordis war, und 9 mal auf Lungenemphysem.

Von den untersuchten 11 deutlichen Polyzythämiefällen wiesen zwei Thrombosen auf, und zwar der eine in den Lungen, der andere im Gehirn. In beiden war die Polyzythämie durch einen angeborenen Herzfehler hervorgerufen. Blutungen hatte keiner. Durch die Polyzythämie verursachter Kopfschmerz kam bei zwei durch einen erworbenen inkompenzierten Herzfehler hervorgerufenen Fällen vor. Zwei der weiblichen Patienten, deren es in dieser Gruppe zusammen sechs gab, hatten eine offenbar auf innersekretorischen Störungen beruhende Schwächung der Menstruationen. Sonstige innersekretorische Störungen wurden nicht festgestellt.

Deutliche Zyanose wurde bei 10 Patienten konstatiert, bei einem Mann, der an durch einen erworbenen inkompenzierten Herzfehler ausgelöster Polyzythämie litt, war die Farbe der Haut dagegen röter als gewöhnlich. In allen 11 Fällen war ein Herzfehler vorhanden, und zwar auch in denen, wo die Polyzythämie augenscheinlich durch Lungenemphysem hervorgerufen war. In den peripherischen Blutgefässen hatten drei arteriosklerotische Veränderungen. Der Blutdruck war bei vier ganz leicht erhöht, der grösste Wert war 160 mm Hg. Bei den anderen war der Blutdruck normal. Die Milz war bei keinem vergrössert.

Die Zunahme des Hämoglobins war mit ein paar ganz unwesentlichen Ausnahmen proportional der Erhöhung der Erythrozytenzahl, so dass der Färbeindex normal blieb. Bei drei Patienten trat eine ganz deutliche, bei einem ausserdem eine leichte Leukozytose auf. Bei zwei von diesen war die absolute Menge der Lymphozyten ein wenig angestiegen, jedoch nicht in dem Masse, dass sie allein die entstandene Leukozytose zu erklären vermocht hätte. Bei den anderen war die absolute Menge der Lymphozyten normal. Bei einem fanden sich im Blute Jugendformen der neutrophilen Leukozyten und bei einem anderen Myelozyten. Jugendformen der Erythrozyten hatte dagegen keiner im Blute. Drei hatten eine deutliche Eosinophilie.

Die Senkungsreaktion war in sieben Fällen während der ersten Stunde unter 1 mm, in zwei Fällen war sie, wahrscheinlich infolge einer gleichzeitigen Infektion, höher, und in zwei ist sie nicht bestimmt worden. Der Ikterusindex nach Meulengracht wurde nur bei drei Patienten bestimmt; bei einem war er normal, bei zwei deutlich erhöht.

Der Grundumsatz wurde nur bei der an der Ayerzaschen Krankheit leidenden Patientin untersucht und leicht erhöht gefunden. Die bei derselben Patientin ausgeführte Bestimmung des Blutkalkes gab ein normales Resultat. Eine deutliche Nephritis hatten zwei Patienten.

Aus den Fällen dürften folgende Schlüsse gezogen werden können:

Die grössten Zahlenwerte der Polycythaemia symptomatica kommen in Verbindung mit angeborenen Herzfehlern vor, besonders wenn sich an den Herzfehler Herzinsuffizienz anschliesst.

Ein kompensierter Mitralfehler oder ein anderer kompensierter Klappenfehler ruft im allgemeinen keine Polycythaemia symptomatica hervor und führt nur selten zu auch nur leicht erhöhten Erythrozytenwerten. Beide kommen dagegen im Zusammenhang mit Herzinsuffizienz vor.

Ein inkompensierter Mitralfehler löst relativ häufiger Polycythaemia symptomatica aus als inkompensierte Myodegeneratio cordis.

Die durch Herzinsuffizienz verursachte Polycythaemia symptomatica verschwindet gänzlich oder nimmt wenigstens bedeutend ab, wenn die Herzinsuffizienz bis zu vollständiger Kompensation behandelt wird.

Lungenemphysem ruft Polycythaemia symptomatica nur dann hervor, wenn es in schwerer Form auftritt, wobei sich daraus auch eine Insuffizienz der rechten Herzhälfte ergeben hat. Es wird durch Therapie nicht ganz zum Verschwinden gebracht.

Manche für Polycythaemia essentialis typische Symptome, wie Thrombosen, Blutungen, Kopfschmerz, innersekretorische Störungen, rote Farbe der Haut, Vergrößerung der Milz, Leukozytose, Auftreten von Jugendformen der Blutkörperchen im Blute, niedrige Senkungsreaktion und Nephritis, sind bei Polycythaemia symptomatica viel seltener, wenn die Erythrozytenzahl auch bei beiden gleich hoch angestiegen sein sollte. Die meisten dieser Symptome sind jedoch in manchen Fällen von Polycythaemia symptomatica zu finden. Die Blutungen und die Vergrößerung der Milz waren die einzigen, die in allen Polycythaemia symptomatica-Fällen meines Materials vermisst wurden. Die niedrige Senkungsreaktion war hinwieder das konstanteste Symptom meines Materials.

#### Schrifttum.

- Bert, P.: Compt. rend. Acad. de Sc. 1882: 94: 805. — Bloom, William: Handbook of Hematology. 1938: 1: 373. — Ehrström, M. Ch.: Finska Läk. sällsk. Hdl. 1935: 78: 105. — Ehrström, R.: Nord. med. Tskr. 1932: 4: 685. — Harrop, Jr., George A. und Wintrobe, Maxwell, M.: Handbook of Hematology. 1938: 4: 2361. — Hirschfeld, H.: Klin. Wschr. 1907: 44: 1302. — Isaacs, R.: Fol. haemat. Z. org. 1922: 22: 134. — Malassez: Ref. nach Harrop und Wintrobe. — Mayers, L. H.: Ref. nach Harrop und Wintrobe. — Morse, P. R.: Ref. nach Harrop und Wintrobe. — Naunyn: Ref. nach Harrop und Wintrobe. — Osler, W.: Brit. Med. Journ. 1904: 1: 121. — Rogers, L.: Ref. nach Harrop und Wintrobe. — Schulten, Hans: Lehrbuch der klinischen Hämatologie, Leipzig 1943. — Seuderling, Y.: Duodecim 1937: 53: 815. — Türk, W.: Wien. klin. Wschr. 1904: 17: 153. — Uhlenbruck, Paul: Die Herzkrankheiten im Röntgenbild und Elektrokardiogramm. Leipzig 1936. — Vaquez, H.: C. r. Soc. Biol. 1892: 4: 384. — Viault, F.: C. r. Acad. de Sc. 1890: 111: 917. — Vogel: Ref. nach Harrop und Wintrobe. — Wintrobe, Maxwell, M.: Ref. nach Harrop und Wintrobe.
-





## Ouvrages envoyés aux *Acta medica Scandinavica*.

*Otmar Frhr. von Verschuer*: Erbpathologie. Ein Lehrbuch für Ärzte und Medizinstudierende. 3. neubearbeitete Auflage. 210 S. 39 Abb. Medizinische Praxis. Band 18. Preis: geh. RM 8: —, geb. RM 9.20. Verlag von Theodor Steinkopff, Dresden und Leipzig, 1945.

*Ligue des sociétés de la Croix-Rouge*: Renseignements scientifiques d'hygiène, médecine et biologie, nos 3 & 4. Herbert Lang & Cie, Berne, 1944.

*Contributions from the University Institute for General Pathology, Copenhagen*. Volume XXI, 1942—1943. Ejnar Munksgaard, Copenhagen, 1944.

---



## On the Effect of Oxygen-want and the Conditions for its Occurrence in Chronic Affections of the Lung.

By

Med.lic. G. BIRATH, Stockholm.

(Submitted for publication June 1, 1944)

---

From the many different pulmonary function tests in clinical practice, either we obtain a measure of some single factor of importance for the respiration, e.g. the vital capacity, or else the result is due to a complex of different variants, making it difficult to reproduce the tests exactly and thus considerably reducing their value (e.g. the apnoeic pause). This applies also to a certain extent to the estimations of the blood gases, though here one does in any case obtain a certain idea of the elementary function of the lung — to enable gas-exchange —; and especially should investigations of the oxygenation of the blood in the lungs be able to give some idea of the lung-function.

In normal circumstances, the upper limit for the working capacity of the organism is set by the work done by the heart, expressed as the cardiac output. This holds good, however, only on condition that the respiratory apparatus is not insufficient, for if this is the case it is the degree of this insufficiency that sets the limit

for the taking up of oxygen. If the organism is pressed beyond this limit, an oxygen-want will arise. It proves, however, that in certain circumstances one can find such an oxygen-want even in the state of rest, in particular in connection with certain morbid states that will be dealt with in the following.

### The symptoms of oxygen-want.

The effect of a deficient supply of oxygen has interested physiologists ever since Paul Bert (1878) described the course of events in a balloon accident in which only one of the crew survived, being thus able to give an account of the symptoms shown by himself and his companions in connection with the increasing rarification of the atmosphere. It is striking to note how the minds of all were dominated by euphoria. Although the balloon continued implacably to rise, the crew felt only glad and happy. Even when exhaustion reached a point at which they could not even move their arms, they felt no fear in face of the perilous situation. — Haldane (1935) also emphasizes this euphoria as a particularly important symptom in connection with oxygen-want.

To this are then added other symptoms. Of the cerebral functions, the memory is the first to be affected. Then the judgement becomes confused, and co-ordination is rendered increasingly difficult. The perception of pain becomes blunted. A patient with these symptoms may in many ways resemble an intoxicated man, with unmotivated laughter or tears, acts of violence and so on. Psychotic states are not uncommon. When aviators and divers in this state lose their sense of judgement their situation may of course become exceedingly dangerous. An incident is told about an airman who after a lengthy raid at an altitude of 6000 meters met a group of enemy fighters. He steered recklessly in among them, waved cheerfully and continued on his way home. It was not until after he had landed that he realized the danger he had been in.

The clinical observations of oxygen-want are relatively few. Since the introduction of arterial puncture as a method of clinical investigation it has been chiefly the pneumonias that among the investigated illnesses have shown any pronounced oxygen-want. In Meakins' and Davies' (1925) list of 15 cases with this disease one

finds that where the lowest oxygen-saturation in the blood was observed, about 80—85 %, there occurred also, almost invariably, cerebral symptoms (normal values, as we know, are about 94—97 %). It is, however, impossible in these cases to decide what rôle is to be ascribed to the toxic effect in the origin of the symptoms, and what is to be put down to oxygen-want.

But even if one is also unable to adduce a direct determination of the oxygen-saturation of the blood, one knows from experience that in connection with a number of diseases oxygen-want can give rise to cerebral symptoms similar to those described above. This is perhaps best illustrated by the final stage in many cases of tuberculosis of the lungs, where the pulmonary tissue may be reduced to a minimum, and an oxygen-hunger may easily be observed from other symptoms. The typical euphoria and the relatively common psychotic states of precisely such patients are thus very conceivably in a greater or lesser degree caused by the oxygen-want. The same applies in the case of the so-called asystolic psychoses, where the oxygen-want is due to the failing activity of the heart.

When on some occasions in connection with acute diseases we have obtained values of 80 % or lower for the oxygen-saturation of the blood, these have always been accompanied by more or less pronounced cerebral symptoms, even if only lassitude and headache.

It must, however, be observed here that the degree of saturation of the arterial blood is not altogether reliable as a criterion of the oxygen supply to the tissues. What is decisive in this connection is the oxygen tension in the capillaries; but this factor is so difficult of access that one is obliged to content oneself with the ordinary saturation values. But one can thus not always expect to find a complete correlation between the symptoms of oxygen-want and the oxygen saturation of the arterial blood, to which I will return later.

Besides the above-mentioned cerebral disturbances, a distinct effect on the circulation and the breathing is also to be observed. In order to compensate the diminished oxygen supply to the blood, the heart increases the rate of the circulation of the blood. It is, however, only in cases of a rather considerably reduced oxygenation of the blood (83 % according to Grollman-Bauman 1935), corresponding to an oxygen-concentration in the inspired air of 11—12 %, that such an increased cardiac output has been defi-

nately established. It is, though, possible at a much earlier stage to demonstrate an increase in the pulse frequency without rise of the cardiac output. This means, then, that even a slight oxygen-want entails increased work for the heart.

As regards the respiration, it is now known — and not least thanks to the contributions of Swedish researchers — that the oxygen-want, or rather, a diminishing of the oxygen tension of the blood, has a stimulating effect on the respiration. The impulses to the respiratory centre are here conveyed by chemo-receptors in glomus caroticum et aorticum. However, a considerable diminution in the oxygen tension is required for an increase in the ventilation to arise. If one successively reduces the oxygen-content in the inspired air one must as a rule, with normal subjects, go down as far as 14 % before a slight increase can be demonstrated, or in other words, to  $\frac{2}{3}$  of the normal oxygen tension in the air. The reaction varies a good deal from individual to individual. The increase that one obtains is at the most about 50—100 % of the total ventilation, and is thus incomparably less than the rise in the ventilation that can be brought about by carbon dioxide.

The reactions mentioned above refer to acute oxygen-want. The case is otherwise in connection with the chronic oxygen-want that one finds in persons who have been exposed to low atmospheric pressure for any length of time, e.g. in those living at an altitude of a couple of thousand meters. In such cases one finds that in different ways an adaptation has taken place that has considerably modified the reaction of the organism. It is of course very probable, and in certain respects also known, that a similar adaptation occurs in connection with the diseases that may give rise to a chronic oxygen-want, and one must therefore in these cases not expect the pronounced symptoms that characterize acute oxygen-want.

The significance of the stimulating effect of oxygen-want on the respiration and the circulation has been made the subject of special interest from the clinical point of view by the Brauer school in Germany. Cf., for example, Brauer (1940), Knipping (1938), Petzold (1939). What has been especially emphasized is the risk of a defective oxygenation of the blood during collapse therapy, as the result then might be jeopardized by the increased demands on the lungs and heart to which the oxygen-want gives rise. If one carries e.g. a bilateral pneumothorax treatment too far, it leads to oxygen-

want — at least if the patient is working — and it thus has an unfavourable effect on the healing process in the lungs and on the cardiac musculature, where in more aggravated cases it is even possible that myocardiac lesions may result.

In order to ascertain when oxygen-want exists one does not employ arterial puncture and blood gas analysis, one simply determines the oxygen consumption with an ordinary spirometer, that contains first air, then pure oxygen-gas. If the oxygen consumption in oxygen-gas exceeds that in air by a certain value, then oxygen-want is considered to be established. The method is however, open to serious objections, and the results are thus uncertain; but it is obvious that the idea of the method is a trend in the right direction, and in actual practice, at least in this country, similar lines have been followed without any tests being taken to investigate the oxygenation of the blood. —

An obvious reflection is that an oxygen-want — if it is at all pronounced — might be expected to find expression in a cyanosis. This is however, not always the case.

In the first place, a considerable reduction of the arterial oxygen saturation may occur without a distinct cyanosis. Instead, one finds a greyish pale colour, that from experience we designate as a *signum mali ominis*, and that is probably due to a contraction of the most superficial vessels that prevents the capillary blood from lending colour to the skin to any extent worth mentioning.

And in the second place an actual oxygen-want may also occur in the tissues, even if the hemoglobin proves to be fully saturated. For if the oxygen is uncommonly fast bound to the hemoglobin it does not much signify that fully oxygenated blood circulates in the body, as the latter's oxygen requirements will nevertheless not be satisfied. Such a condition arises if for example the  $\text{CO}_2$ -tension in the blood is for some reason or other reduced, generally on account of hyper-ventilation (so-called Bohr-effect). Such actual hyper-ventilation may be conceived as occurring either in connection with bilateral pneumothorax, where it has proved that the ventilation of the functioning parts of the lung is very effective even in the state of rest. This might explain why in spite of considerable dyspnoea such a patient is seldom cyanotic.

It is also possible that we have here one of the causes of the difficulty experienced by these patients in maintaining their nor-



mal weight. With a chronic oxygen-want in the tissues it is of course easy to understand why their vitality suffers. It must, however, be emphasized that there are no investigations to be adduced in proof of the assumptions made here.

### Causes of oxygen-want.

If we except the last-mentioned special form of oxygen-want with saturated hemoglobin, it is characteristic for the oxygen-want of pulmonary origin that the blood, after its passage through the lungs, has not become fully oxygenated. Theoretically, this may be explained in the light of one or more of the following three causes:

1. Impaired diffusion through the alveolar epithelium.
2. Changes in the pulmonary circulation with admixture of venous or insufficiently oxygenated blood.
3. Impaired pulmonary ventilation with reduction of the oxygen tension in the alveolar air.

ad. 1. Impaired diffusion through the alveolar membrane — by Brauer referred to as pneumonosis — probably arises through the effect of toxic substances or whenever an alveolar oedema exists. We do not yet know sufficient to determine whether or not this condition is of particular clinical importance. The direct determinations of the diffusion-constant carried out by M. Krogh on some cases of emphysema and pneumonia gave normal values. As regards the tuberculosis clientèle, in any case, one probably does not need to reckon with this cause of defective oxygenation.

ad 2. It is, on the other hand, by no means uncommon for venous blood that has passed through non-ventilated parts of the lungs to become mixed with the oxygenated blood and in this way reduce the arterial oxygen-saturation. This process, that thus withdraws the blood from the normal gas-exchange, has been compared to a short circuit, and it is also generally referred to in the literature as »Kurzschluss» or »shunting». In atelectasis it is in precisely this way that one can attain a certain reduction in the oxygen-saturation. Especially during the first period after the formation of an atelectasis a certain amount of blood passes through the atelectatic tissue; but the circulation very soon adapts itself, and then no very pronounced shunting occurs. Berggren (1942) has in some cases and with an extremely accurate method been able

to measure the effect on the oxygen-saturation of the blood that a shunting can in itself entail. In one case with complete atelectasis of the inferior lobe, that arose post-operatively, Berggren found, the day after the development of the condition, a reduction in the oxygen-saturation due to shunting corresponding to 6.6 % unsaturation, the day following, 3.5 %, and on the fourth day, when the atelectasis had disappeared, 0.6 %, or the normal value for a patient confined to bed. If the circulation in the atelectatic part had continued unchanged, the blood would have been saturated, on leaving the lungs, to a degree of only about 80 %, or in other words, the reduction would have been about 20 %.

An older atelectasis in a collapsed lung, on the other hand, has a still more reduced circulation, and its effect on the oxygen-saturation of the arterial blood is thus less. Even a completely atelectatic collapsed lung, according to Berggren's investigations, gives through shunting a reduction in the oxygen-saturation of scarcely more than approximately 5 %, in general perhaps even less. The shunting that is brought about in the atelectatic part underneath a thoracoplasty gave in four of the cases examined by Berggren a reduction of the oxygen-saturation of between 1 and 3 %, thus quite an insignificant effect. My own results have the same trend (will be published later).

An interesting case, that illustrates this shunting mechanism, has been examined by me in the medical tuberculosis department of St. Göran's Hospital. The patient was a woman of twenty years who had a bilateral lung-tuberculosis with a right-sided pneumothorax artificialis (Fig. 1). She frequently complained of difficulty in breathing before the fillings. On one occasion, owing to particular circumstances, there was a longer interval than usual between the fillings. Towards the end of this period she was complaining daily of a weight and pressure on the breast and of dyspnœa. At the same time it was apparent that she was suffering from increasing cyanosis. The arterial oxygen-saturation proved to be only 79 %, an unusually low value. Two days later, immediately before the insufflation, it was 78 %. After the insufflation of 700 cm<sup>3</sup> (initial pressure —14, —8 and final pressure —8, —4) there was an immediate subjective relief; the cyanosis disappeared almost entirely, and a few minutes after the insufflation the oxygen-saturation had risen to 87 %. Objectively, a decrease in the ventilation from 9.3 to 7.7 lit. per min. was registered, and in the respiratory frequency from 34 to 25 per minute. The explanation of the course taken by the above-described case (probably not at all infrequent in milder forms) that occurred to me was the following: When the lung expands and is exposed to strong suction, collapsed vessels are gradually



Fig. 1.

opened within the (obstruction-) atelectatic parts and allow the passage of blood that has not been oxygenated. In this way the oxygen-saturation of the arterial blood is reduced. When insufflation of air is carried out and the strong negative pressure in the pleural cavity is relieved, these opened vessels collapse once more, and the oxygen-saturation rises.

ad 3. The third possible cause of defective oxygenation of the blood is an impaired ventilation.

If the prototype of the shunting mechanism is the atelectasis, the bronchostenoses and emphysemas are the most characteristic diseases with impaired ventilation. With the bronchostenoses, if one so desires, one may include bronchial asthma, with its multiple bronchial constrictions.

In order to be able to compare the ventilation conditions in different diseases of the lungs we have for some time been employing

RELATIVE INCREASE (=R)  
OF THE HYDROGEN  
IN THE LUNGS

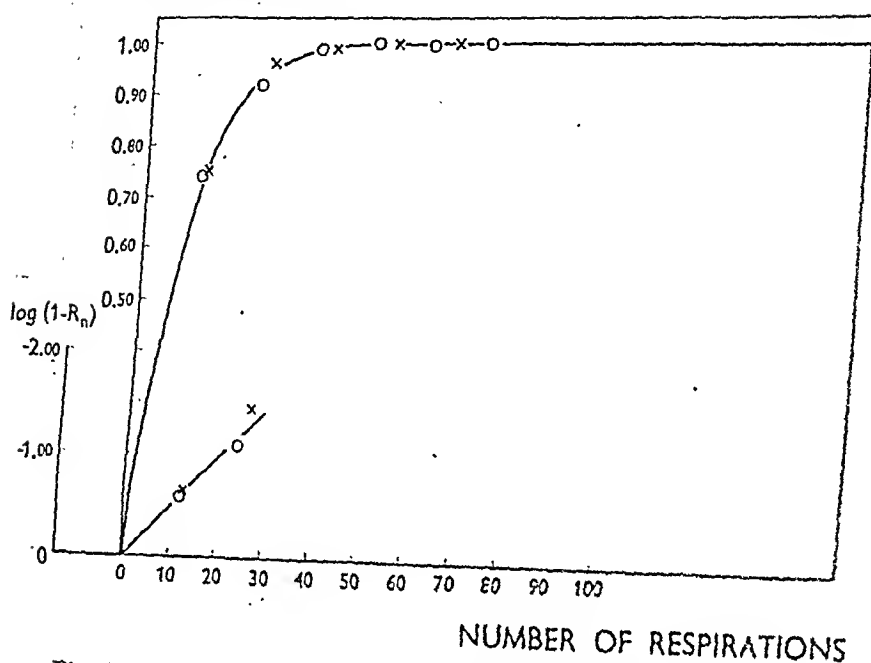


Fig. 2. Double determination of the D.S.-value in a normal male.

○ = first determination D.S. = 0.12 lit.

× = second determination D.S. = 0.18 lit.

a special method at St. Görän's Hospital (Birath 1944). The patient is made to breathe in a spirometer with an excess of oxygen and a known hydrogen concentration. One then follows with regular tests the rapidity with which the hydrogen-gas is drawn into the lungs when the patient is breathing normally. With the arrangements employed by us the normal time for such a test is less than 2 or at the most 3 minutes. For an asthmatic patient, even without rhonchi, it may take up to 10–15 minutes. In cases of emphysema it takes about 4–6 minutes. It is of particular interest to see how effective the ventilation is in connection with bilateral pneumothorax. Here, the mixture of hydrogen-gas and lung-air is as a rule complete before one minute has elapsed.

On the basis of the values of the hydrogen concentration obtained at minute intervals and with a knowledge of the volume of the spirometer system on the occasion of each test, it is possible to calculate the volume of hydrogen that has been drawn into the

RELATIVE INCREASE ( $-R$ )  
OF THE HYDROGEN  
IN THE LUNGS

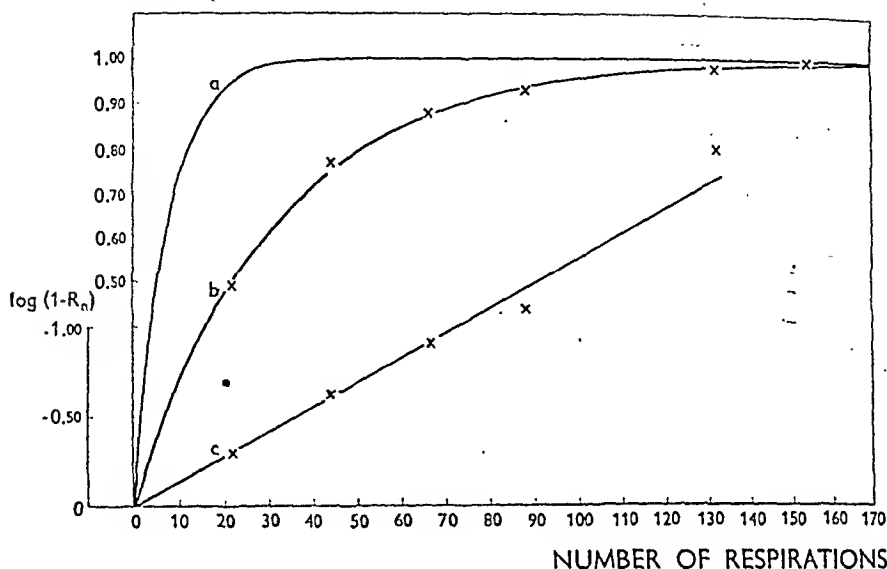


Fig. 3. Determination of the D.S.-value in a case of pulmonary tuberculosis with thoracoplasty and emphysema.

a = ventilation curve calculated. Presumed D.S. = 0,15 lit.

b = ventilation curve found. D.S. = 0,30 lit.

c = log curve of b.

lungs at the point of time in question. This volume finally becomes constant, and is then equal to the lung-volume with which the subject of the experiment is breathing at the time. As one now knows the volume of the lungs in the position of equilibrium, the tidal volume and the volume of the spirometer system, it is possible to calculate with what respiratory dead-space (D.S.) the ventilation would take the course observed. The value for the dead-space thus obtained proves as regards healthy lungs to agree, on the whole, with the current measurements, that for breathing in a resting position are more or less uniform with different methods. (See fig. 2).

If one calculates in the same way the «dead-space» for pathological cases of various kinds one frequently gets considerably heightened values. They are, indeed, sometimes so high that the taking up of oxygen would be impossible to the extent that is necessary already in a position of rest, if the actual dead-space really had this magnitude. This, however, is not the case, for what one is determining here is not only the effective dead-space. One also finds an



Fig. 4.

addition to the real dead-space, owing to a delay in the ventilation, brought about in its turn by a reduced ventilation in certain parts of the lungs. How badly the ventilation here in question may be impaired is best seen if for comparison one calculates the course of the ventilation for a dead-space of normal magnitude, as in fig. 3. Radiography of the lungs in the same case in fig. 4.

With this method it is thus possible to get an idea of the extent to which the parenchyma as a whole is normally ventilated. Among others, Sonne (1934) and his co-workers have advanced a theory concerning an uneven ventilation of the normal lung. In our investigations it does not appear to be of any particular importance in healthy lungs, as one seems here to obtain normal values for the dead-space; but in cases of asthma and emphysema and in a great

number of cases of tuberculosis, on the other hand, it is very pronounced.

If, now, certain parts of the lungs are badly ventilated, the circulation seems to adapt itself accordingly, so that these parts have a blood circulation reduced according to the degree of ventilation (Matthes 1940, Roelsen 1937). This is the explanation of the fact that despite large badly ventilated regions in the lungs, one does not find any marked reduction of the arterial saturation. Silicosis patients, for instance, often have when resting a normal saturation (Bruce 1942), despite a considerable impairment of the ventilation in certain parts of the lungs.

Also in connection with pneumothorax one finds an adaptation of the circulation to the often reduced ventilation, and this is the explanation of the fact that one does not find any marked reduction of the oxygen-saturation in the blood in these cases. The rate of the blood-stream, or in other words the cardiac output, is, however, practically unchanged. This means that since the circulation in the pneumothorax lung is considerably reduced, the contra-lateral lung gets a corresponding increase in the amount of circulating blood. As in the muscle during work, it is evident that reserve capillaries that otherwise, during rest, are collapsed, then open and allow the passage of the increased blood-stream. This, then, is the physiological basis of the increased vascular shadowing we observe in the contra-lateral lung. This has been very beautifully shown by Lopo de Carvalho (1940) by means of the injection of a contrast solution in the pulmonary circulation and earlier by A. F. Lindblom (1930).

In some cases the oxygen-saturation of the arterial blood has been examined according to v. Slyke-Neill before and after hyper-ventilation, in the belief that a possible oxygen deficit due to hypo-ventilation would then disappear, if it had not already been compensated by a diminished circulation. As may be seen in table 1, every case shows an increase in the oxygen-saturation, probably on account of, firstly, the heightened oxygen-tension in the alveoles, and secondly, a shifting of the dissociation-curve of the hemoglobin «to the left» through the hyper-ventilation.

That the latter factor should entail a greater increase in the oxygen-saturation in those cases that were lower saturated from the outset (below 94 %) than in the normally saturated cases is no more than one might a priori expect. When, then, one finds that

Table 1.  
Changes of the blood gases by hyper-ventilation.

Number	Age	Sex	Diagnosis	Rest				After 3 min. hyper-ventilation			
				Vol. per cent. O <sub>2</sub>	Vol. per cent. O <sub>2</sub> - capacity	Per cent. O <sub>2</sub> - saturation	Vol. per cent. CO <sub>2</sub>	Vol. per cent. O <sub>2</sub>	Vol. per cent. O <sub>2</sub> - capacity	Per cent. O <sub>2</sub> - saturation	Vol. per cent. CO <sub>2</sub>
1	39	♀	Pulm. tbc.	17.4	18.5	94.1	47.1	16.8	17.5	96.0	44.55
2	19	♀	»	21.35	22.2	96.2	46.4	20.9	21.65	97.2	39.85
3	18	♀	D:o + unilat.	17.0	19.3	88.1	39.5	16.95	18.8	90.2	36.05
4	29	♀	pntx	19.75	21.35	92.5	45.95	19.75	20.85	94.7	41.0
5	28	♂	»	19.4	20.8	93.3	46.2	20.4	20.7	98.5	38.9
6	35	♂	»	19.4	20.85	93.0	44.7	19.7	20.75	94.5	42.45
7	30	♂	»	18.55	19.25	96.4	52.75	18.85	19.3	97.7	45.75
8	41	♀	»	16.75	18.2	92.0	47.05	17.2	18.05	95.3	40.1
9	30	♂	D:o + pntx bilat.	17.75	19.85	88.2	46.25	18.4	19.9	92.5	42.3
10	20	♂	D:o + thora- coplasty	18.55	19.45	95.4	50.15	18.6	19.4	95.9	42.0
11	44	♀	»	14.9	15.45	96.4	49.1	14.9	15.3	97.4	42.6

the former group increases on an average 3.2 % and the latter one 1.1 % the statistically probable difference — calculated with analysis of variance according to Bonnier and Tedin (1940)<sup>1</sup> — is no proof that a poor ventilation entailed the reduction in the saturation observed. The registered increase in saturation is not so great as to preclude the ascription of at least the best part of it to the change in the course of the dissociation-curve.

The above described investigations all refer to the state of rest. Investigations of the oxygenation of the blood in connection with work are — apart from the examinations of healthy persons by physiologists — very few in number. In connection with tuberculosis of the lungs and collapse therapy it would seem that investigations in this respect have been carried out only with the indirect spirometric methods of the Brauer school.

<sup>1</sup> Snedecor's F-test.



Table 2.

Changes of the blood gases during the performance of work.

Number	Age	Sex	Diagnosis	Rest				After 3 min. work			
				Vol. per cent. O <sub>2</sub>	Vol. per cent. O <sub>2</sub> -capacity	Per cent. O <sub>2</sub> -saturation	Vol. per cent. CO <sub>2</sub>	Vol. per cent. O <sub>2</sub>	Vol. per cent. O <sub>2</sub> -capacity	Per cent. O <sub>2</sub> -saturation	Vol. per cent. CO <sub>2</sub>
1	23	♀	Pulm. tbc.	17.6	18.2	96.7	49.0	18.4	18.95	97.1	42.6
2	29	♂	»	16.85	17.4	96.8	49.6	17.1	17.4	98.3	48.2
3	29	♂	»	19.45	20.5	95.1	47.5	19.4	20.65	93.9	41.3
4	28	♂	D:o + unilat. pnthx	17.9	18.7	95.7	48.9	18.65	18.9	98.7	45.4
5	27	♂	»	18.25	19.15	95.3	48.6	18.7	19.3	96.8	44.8
6	32	♂	D:o + bilat. pnthx	18.7	19.65	95.2	47.0	18.5	19.2	96.3	45.1
7	20	♂	»	18.3	19.9	92.4	46.3	18.9	20.65	91.5	46.0
8	27	♂	»	18.4	20.95	87.8	53.3	18.7	21.6	86.6	49.9
9	28	♂	»	17.3	18.1	95.5	48.8	17.9	18.75	95.5	42.9
10	27	♂	»	17.6	18.65	94.4	46.8	17.9	19.15	93.5	42.7
11	23	♂	»	17.8	18.6	95.7	50.6	17.7	18.65	94.9	48.3
12	42	♂	D:o + thora-coplasty	14.75	16.6	88.9	49.2	14.8	16.6	89.2	46.4
13	31	♂	»	16.35	17.4	94.0	50.8	16.1	17.1	94.2	49.1

We have investigated the saturation after light work for 3 minutes (leg movements in bed as in cycling at the rate of one revolution a second). Unfortunately, no very accurate graduation of the work was possible. It would have been desirable for the work to be performed for a longer period, but this was rendered impossible by the state of the patients. However, in the absence of any previous values, the results are given in table 2.

As in the case of the investigations of hyper-ventilation, the samples were taken through a heparinized cannula provided with a tap, that was allowed to remain in the artery, thus enabling the sample to be taken at a definite time. In the experiments with »working» patients the »work» was of course persevered with until the whole sample had been taken. The same applies also to the experiments on hyper-ventilation.

A certain rise in the oxygen-saturation seems also to have occurred here, except in the bilateral pneumothorax cases, where one gets on an average a 0.6 % decrease as compared with a 0.8 % increase in the others. The difference is, however, not statistically certain, and verification must be postponed until a larger observation material becomes available.

### Summary.

It emerges from the investigations that have so far been carried out on the physiological effects of oxygen-want that the latter, at least in a pronounced form, may increase the work of the organs of respiration and circulation. It thus seems that the oxygen-want may in this way have an adverse effect on the healing of disease processes in the lungs, and it should therefore be avoided as far as possible.

Deficient oxygen-saturation of the arterial blood may be caused by

1) impaired diffusion through the alveolar epithelium (so-called pneumonosis);

2) changes in the pulmonary circulation with admixture of venous or insufficiently oxygenated blood (e.g. atelectasis, especially the obstructive type);

3) changes in the lung-ventilation with reduction of the oxygen-tension of the alveolar air (e.g. emphysema, local or general).

The main lines of a new method are given for the investigation of the ventilation-effectivity of the lungs. It is based upon quiet breathing in a closed respiratory system containing a known amount of hydrogen-gas.

In some cases blood-gas determinations have been carried out during hyper-ventilation and during the performance of work. In general, the oxygen-saturation rises in these cases.

### Literature.

- Berggren: *Act. physiol. scand.* Vol. 4. suppl. XI. — Birath: *Acta med. scand.* 1944: suppl. 154. — Bonnier & Tedin: *Biologisk variations-analys.* Stockholm 1940. — Brauer: *Verh. d. deutsch. Ges. f. Kreisf. forsch.* 1940: 13: 37. — Bruce: *Die Silikose als Berufskrankheit in Schwe-*

den. Act. med. scand. 1942: suppl. 129. — de Carvalho: Beitr. z. Kl. d. Tbk. 1940: 95: 262. — Dirken, Kraan, Oostinga & Woudstra: Act. med. scand. 1942: 109: 514. — Grollman-Bauman: Schlagvolumen und Zeitvolumen, Dresden und Leipzig 1935. — Grosse-Brockhoff, Schoedel & Springorum: Pflüger's Arch. f. Physiol. 1936—37: 238: 501. — Haldane & Priestley: Respiration, Oxford 1935. — Knipping: Beitr. z. Kl. d. Tbk.forsch. 1938: 92: 144. — M. Krogh: Luftdiffusionen gennem Menneskets Lunger. Diss. Copenhagen 1914. — A. F. Lindblom: Act. med. scand. 1930: 73: 493. — Matthes: Verh. d. deutsch. Ges. f. Kreisl.forsch. 1940: 13: 107. — Meakins & Davies: Respiratory Function in Disease, Edinburgh 1925. — Miller & Whitehead: Am. Rev. of Tbc. 1940: 41: 1. — Peters and v. Slyke: Quantitative Clinical Chemistry. London 1931. — Petzold: Beitr. z. Kl. d. Tbk.forsch. 1939: 92: 635. — Roelsen: Fraktionel Alveole-luftanalyse. Diss. Copenhagen 1937. — Sonne: Act. med.scand. 1934: suppl. 59.

---

From the St. Joseph's Hospital, Porsgrunn, Norway.  
Physician-in-Chief August Schrumph.

## Felty's Syndrome: Splenomegalia, Leucopenia and Chronic Polyarthritis. — Familial Occurrence.

By

JOHANNES ZIMMER.

(Submitted for publication October 23, 1944).

---

### *Historical Review.*

The American A. R. Felty (19) in 1924 published five cases of «an unusual clinical syndrome», characterized by: 1) chronic progressive polyarthritis. 2) leucopenia, partially with marked neutropenia, and 3) splenomegalia. His cases consisted of men and women between forty-five to sixty years of age. Besides the above mentioned triad of symptoms was also found individually pigmentation of the skin, swollen lymphatic glands and urobilinuria. All patients showed a gradual decline of health from year to year. They showed considerable loss of weight and hypochromic anemia. In one case where the number of thrombocytes were counted, the result showed a physiological value.

Apparently syndroma Felty (S. F.) has been little noticed and mentioned in the world literature. The author has been able to trace only thirty definite cases.

Fifteen cases from America have been published from 1932 to 1936. In Europe the syndrome is mentioned for the first time by Allesandrini (2) in 1934 as «la splenomegalie arthropatissante». Subsequently single cases have been published, particularly from Germany. In Scandinavia the first case was published from Denmark by Gyntelberg (23) in 1942, shortly

afterwards another case by Trolle and Trolle (70). From Sweden we have two cases. [Ekelund (17)]. From Norway as yet no case has been published.

### *Symptoms.*

According to the generally accepted view S. F. consists of the three mentioned main symptoms, and the inconstant symptoms, such as skin pigmentation, swollen lymphatic glands, urobilinuria and enlarged liver. The latter is rarely seen [Breu and Fleischhacker, (9), Craven jr. (11), Hanrahan and Miller (26), Gyntelberg, (23)], nor a reduced liver function [Craven jr (11)]. The disease attacks middle-aged individuals, especially women.

Characteristic is the insidious chronic lesion of the joints, lasting for years, — with acute exacerbations and fever — which may affect all the joints, though particularly those of the fingers, hands, ankles and knees. With the years the joints may become deformed making the patient an invalid. This is not a frequent occurrence, however.

Roentgenologically one finds in the joints, besides swelling of the soft tissue also affection of the bony parts. [Breu and Fleischhacker (9) and others]. The articular space becomes more narrow, the outlines of the joints blurred, decalcification appears and fissures may be seen. In later stages subluxations may occur.

At first the general health is little influenced, but is affected after years, with loss of weight and disposition to secondary infections. Spontaneous recovery is not described.

Very often the previous history gives information of infection in the mouth, throat and tonsils. Likewise is mentioned carious teeth with infectious foci in the jaw, and pyorrhoea. These infections are always forerunners of the polyarthritis, which is emphasized particularly by Breu and Fleischhacker (9).

In some cases the polyarthritis starts acutely, more often, however, insidiously.

The splenomegalia may be prominent, with the lower splenic border at or below the umbilical transversal. In some cases the spleen is scarcely palpable. This viscus usually is unsensitive. Pain in the splenic region occurs, most frequently in attacks in connection with an acute exacerbation of the lesion.

*The leucocyte values* are seldom over 3000 per cubic millimetre, and the leucopenia usually is *chronic*, with little variation in the leucocyte figure. Ekelund (17) found in his two cases down to 300, respectively 400 leucocytes, which is extremely low, especially as both patients were in comparatively good condition. He emphasizes as worth noticing, therefore, that the general condition in *chronic* granulocytopenia with a low leucocyte figure is relatively not so much influenced as with corresponding values in *acute* agranulocytosis. — In the few cases of acute agranulocytosis during

the course of S. F., which have been reported, increase of the leucocytes was noticed when the ulcerations healed. Later on the leucocytes decreased to a low value and remained there. [Fleischhaecker and Lachnit (21)].

In a number of cases *eosinophilia* has been noticed. Up to 13 per cent has been reported [Felty (19)]. Craven jr. (11) makes a closer comment on this. In his one case the eosinophilia persisted after splenectomy. It decreased, however, from twelve to six per cent. The same author emphasizes the not unusual finding of *eosinophilia, chronic arthritis and leucopenia*. Worth mentioning is that the American Harrison (27) has reported splenomegalia and eosinophilia as a separate syndrome.

As a rule a *marked lymphocytosis* occurs with S. F. The concurrent *anemia* frequently is a *hypochromic one*, with average hemoglobin values of from 60 to 80 per cent.

Thrombocytopenia does not occur constantly. Values between 100,000 to 200,000 per cubic millimetre is the usual finding if thrombocytopenia is present (lowest value 42,000). Hemorrhagic diathesis seldom occurs. The *sedimentation rate* often shows highly increased values. —

*The bone marrow:* Approximately one-third of the definite cases was examined by marrow puncture. Most of the authors found a hyperplastic bone marrow with lively erythropoiesis (highly increased number of erythroblasts). The thrombopoiesis usually is intact. The characteristic and most constant finding is a *maturation arrest in the granulocytopoiesis*, most frequently after the myelocyte phase. Highly decreased numbers of segmented forms are always seen, — even total disappearance. At the same time is found an increase of the more immature cell forms, mostly of promyelocytes and myelocytes.

This bone marrow picture corresponds to the picture seen in granulocytopenia with a *chronic course*. A similar picture may be seen also in infections, according to the severity of which is found a gradual increase (or later on decrease) of the immature cells, and at the same time a maturation arrest in the granulocytopoiesis, with hyperplasia [Nordenson (45)].

*Blood cultures* most frequently have given a negative result in S.F. Singer (64) was the first to report a positive result viz. streptococcus viridans (two cases).

In several other cases streptococci have been demonstrated, though occasionally also other bacteria, such as typhoid bacilli, gonococci and enterococci. In cultures from the spleen Singer and Levy (65) found streptococcus viridans, likewise in the tonsils of the same patient. Craven jr. (11) found growth of green streptococci from lymphatic glands.

*Pathologic anatomy.*

Price and Schoenfeld (52) (according to Breu and Fleischhacker) describe the first post mortem findings. They demonstrated in liver and spleen signs of chronic infection, but »nothing specific». Subsequent spleen examinations verify this latter. Curtis and Pollard (12) in muscular tissue and blood vessels from patients suffering from chronic rheumatism and S. F. demonstrated the same changes which are typical of rheumatic arthritis. In the joints are seen the same changes as in chronic polyarthritis [Breu and Fleischhacker (9)].

*Etiology.*

The etiology according to the above is considered to be infectious, presumably caused by streptococci of the viridans type, — occasionally by other bacteria. In accordance with this S. F. is regarded as a sepsis of chronic type [Curtis and Pollard (12)]. The many negative blood cultures, the relatively good condition for numbers of years, and the long duration of life speak against a virulent bacterial infection.

The so-called Still-Chauffard's disease (67) (S.-Ch.), first described by Chauffard and Ramond (10) in 1896, which progresses with arthritis, hypertrophy of glands and spleen, and anemia, shows great similarity to S. F., which Felty (19) pointed out himself, and after him many others.

One discrepancy is the age, as S.-Ch. affects children before the second decennium, S. F. adults only; another is the duration of the disease: numbers of years in S. F., considerably shorter in S.-Ch. The later lesion often is cured, S. F. not. In S.-Ch. a moderate leucocytosis frequently is seen, which has to be regarded as a *relative leucopenia* in relation to the septic condition [Leichtentritt (35)].

The bacterial findings in S.-Ch., as well as in S. F. vary: mostly streptococci. From a pathological-anatomical view there are no data whatever in support of a specific disease. Therefore, S.-Ch. has to be looked upon as a chronic sepsis similar to S.F.

Singer and Levy (65) state: »S. F. is the manifestation of S.-Ch. in adults». These authors by a critical search through the world literature find many publications dealing with S.-Ch., from America as well as from many countries in Europe, among which are hidden

cases of S. F. [Pollitzer (51) describes S.-Ch. as similar to S. F. for the first time in European literature in 1914]. Such *hidden cases* of S. F. mostly have carried titles as «atypical form of morbus Still in adults», or similar ones. Thus, Bren and Fleischhacker (9) traced many cases «with the peculiarity of Felty», — the majority of which from 1927 to 1935 (none from Scandinavia).

Disregarding the polyarthritis, the other symptoms present: the splenomegalia, the anemia, the leucopenia, possibly the urobilinuria, form a picture *similar to Banti's syndrome*, which Felty (19) was the first to point out. Singer (64) also claims that in the world literature a certain number of cases of S. F. are concealed under the terminology «syndroma Banti» or «splenic anemia».

*Conclusion:* S. F. is not a disease reports of which have been published so rarely as the impression given by the literature. The syndrome seems, as pointed out by the above mentioned authors, in several cases to have been concealed under different names.

### *The Justification of the Conception of S. F.*

Felty (19) regarded the constellation splenomegalia, leucopenia, and polyarthritis as unusual. A survey of the literature, however, gives the following information:

1: Mc. Crae (40) in 1914 collected 110 cases of «arthritis deformans» four of which had splenomegalia, eight skin pigmentation thirteen general hypertrophy of the glands, six leucocyte values below 5000 per cubic millimetre. Two patients had Still's disease.

2: Price and Schoenfeld (52) (1934) state that it is not a question of a new picture of disease, without giving any reason for this contention, however.

3: Craven jr (11) (1934) states that the literature contains many records of chronic arthritis, splenomegalia, and leucopenia, without compiling it into a unit, as Felty (19) did in 1924.

4: Singer and Levy (65) (1936) mention the richness in literature of chronic arthritis associated with either hypertrophy of the lymphatic glands, or splenomegalia, or both, — and varying with leucopenia, pigmentation of the skin, secondary anemia, and subcutaneous nodes, — found in adults as well as in children.

5: Fleischhacker and Lachnit (21) (1940) collected 55 cases of



polyarthritis. Eleven showed leucocyte figures below 5000, none below 3000. »The primary chronic polyarthritis showed the lowest leucocyte figure.»

6: Curtis and Pollard (12) (1940) found among patients with chronic rheumatism in a few cases partly S. F., partly only enlargement of the spleen. The pathological-anatomical changes were all typical of rheumatic polyarthritis.

7: Henel (28) emphasizes that one per cent of all »arthritic patients» have splenomegalia (quoted from Singer). Dawson mentions that ten to fifteen per cent of all cases of chronic polyarthritis have splenomegalia.

Bren and Fleischhacker (9) assert, therefore, that it is *the way the patient reacts*, on which depends the occurrence of this syndrome, and not a definite germ. Singer and Levy (65) agree with them, and emphasize that the different clinical symptoms which may arise in connection with chronic arthritis represent different manifestations of the same disease. Through the toxins the underlying infection attacks not only the joints, but also the hematopoietic system, the spleen and the lymphatic glands, — these together or separately, — resulting in different combinations of symptoms. It should then be the different power of resistance of the patient's organs which determines the symptomatology, and the variable clinical picture in chronic arthritis. Occasionally, therefore, a case of S. F. must arise. S. F. will be a special manifestation of rheumatic chronic polyarthritis in adults, in the same way as morbus Still-Chauffard will be such manifestation in children.

As this syndrome, therefore, does not appear to show anything actually new, Dawson (14) is, of of the opinion that the name »Felty» should be avoided. However, the symptom combination that constitutes this syndrome contains so much of interest, not only from a pathogenetical and clinical point of view, *but most of all therapeutically*, that it is probably correct to keep the name the triad has received.

#### *Own Cases.*

*Case 1.:* On January 16, 1942, a female 30 years of age, was admitted to St. Joseph's Hospital, Porsgrunn, under the diagnosis subacute rheumatic fever.

<sup>1</sup> Demonstrated at The Oslo Association of Internal Medicine, June 5, 1944.

*Family history:* It is worth noticing that her mother, one brother and two sisters have undergone a febrile rheumatic articular affection, having had a more or less acute start, with a chronic, insidious course, and frequent relapses. One of the sisters, M. H. (more fully referred to in case two) is an invalid on account of her deforming polyarthritis. An aunt on her father's side also has chronic polyarthritis.

*History of disease:* Healthy until the onset of the present disease about midsummer 1938, with infection of the lower jaw due to infectious dental foci, (greatly defective teeth), and shortly afterwards angina. During a stay at the Telemark County Hospital for 25 days (from July 7. to August 1. 1938) was found, besides large swampy tonsils and a slight hypochromic anemia, leucopenia, showing 2700 white blood cells per cubic millimetre, and 10 per cent segmented forms. *The spleen was hardly palpable.* The case history from the hospital gives the information that during this stay she noticed pain in her finger joints, and later on in her ankles. The angina quickly regressed. The spleen was not palpable on discharge.

On readmission half a year later, due to a submandibular abscess, which arose after extraction of several permanently filled teeth, leucopenia was not demonstrated (5700 white cells), and the segmented forms showed 68 per cent. *The spleen was distinctly felt.*

After this second stay in hospital her disease, the polyarthritis, started in earnest. The joint affection took an insidious course, with remissions and exacerbations. During shorter and longer periods the joints were swollen, at first the finger joints, which became thick, stiff and painful, next followed carpal, shoulder, knee joints, and ankles. During flaring-up of the joint affections she had fever and had to stay in bed for weeks; in the free intervals she performed usual housework. The number of exacerbations increased year by year. It was during such an attack that she was admitted into St. Joseph's Hospital on January 16. 1942.

No definite heart affection may be traced in the anamnesis. Though she never felt quite well the general condition for a relatively long period remained good, though gradually decreasing the last half year before admission. Loss of weight from 1938 to 1942 about 10 kilos. A blood control was never performed during these years; in her opinion she was constantly anemic. A positive information about the size of the spleen after the second stay in the hospital in 1938 is lacking. Icterus has never been observed, nor enlarged lymphatic glands or skin pigmentations. During recent years she has been suffering increasingly from furuncles, especially on the nates. At first they contained pus, later not. No exact date can be given for the cessation of pus formation. According to the estimate of the patient it was presumably about three-quarters of a year ago.

No definite hemorrhagic diathesis has been observed. The menstruation never lasted for more than four days; neither menorrhagia nor metrorrhagia has been present.

*Medication until admission:* There has been a considerable use of sulfanilamide. Before the first hospitalization in 1938 four to six grams, during this stay 66 grams, and in the last five months before the admis-

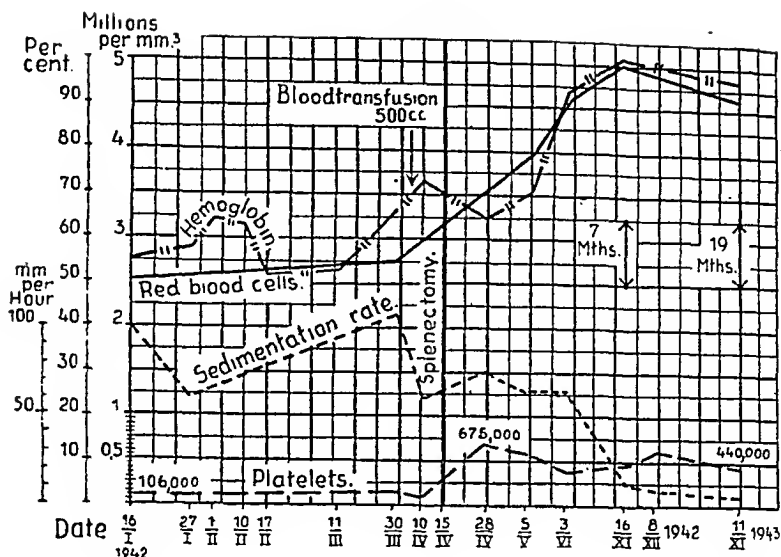


Fig. 1. Case I. Blood examinations in peripheric blood.

sion 65 grams. The total definite dose is 135 grams at least. In addition to this dose comes an unknown quantity, which she herself has administered during these years, and which the patient herself has termed »considerable». Iron has been used only once, viz. during the second stay in hospital in 1938. Other medicaments used have been salicylic acid and laxatives. *Use of amidopyrine may be excluded.*

*Physical examination, January 16, 1942* (most important findings). Thin, pale. No skin pigmentations, no general swelling of lymphatic glands. Submandibularly, however, on both sides were felt several firm, indolent, movable, lymphatic glands, the size of up to a walnut. Below the left lower jaw an old scar after an incision. Teeth lacking.

Pulse: 60 regular. Temperature: 38.9° C., rectal, vesper. Blood pressure: 145/85. No necrotic ulcers in the throat, or elsewhere. Heart: slightly systolic sound, otherwise nothing of importance. Abdomen: A large, even, smooth tumour was found in the left side, reaching from the costal arch to below the umbilical level, of the shape of the spleen. Slightly tender to pressure. The liver: not palpable.

*Local examination:* Skin of hands and fingers bluish-white. Symmetrical, spool-shaped, periarticular swelling of the metacarpo-phalangeal joints, and in a less degree of the proximal finger joints, with subcutaneous, movable rheumatic nodes, and atrophy of the interosseous muscles. No subluxation or ulnar deviation. The carpal joints also showed swelling, and all the above mentioned joints were painful on active movements. The other joints were normal, apart from slight pain in the elbow joints, and the left knee joint. — On the right buttock was seen a furuncle, the size of a walnut, without sign of pus formation.

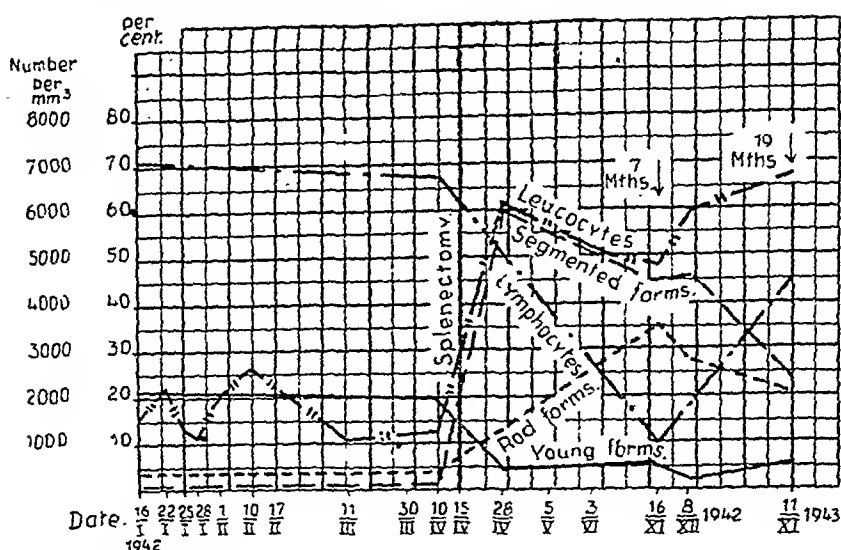


Fig. 2. Case I. Blood examinations in peripheric blood.

Further examinations and the course were as follows:

Urine: physiological. (Ehrlich's test negative.) Meinicke II in blood serum: negative. Serum colour: 7.5. Bleeding time: 3 minutes. Clotting time: 1 minute. Osmotic resistance of the red blood cells: beginning hemolysis at 0.40 (Dec. 8, 1942.) As to divers examinations in the peripheral blood: see figs. 1 and 2. <sup>1</sup> One notices the marked leucopenia with total absence of segmented forms, the anemia, the thrombocytopenia, and the high sedimentation rate.

Bone marrow: hyperplastic, rich in cells; no pathological cell forms. Counted 300 cells. Maturation arrest in the granulocytopoiesis after the metamyelocyte phase with an increase of immature forms, and a lively erythropoiesis (figs. 3 and 4).

January 17. Roentgenological examination of hands: Some osteoporosis, blurred articular outlines, and narrow articular spaces. No sloughing.

The general condition became constantly poorer. Heavy, pressing pain occurred in the splenic region, accompanied by steep rises of temperature up to 40.7° C. Numerous furuncles appeared on the buttocks, not producing any pus. She lost weight. No signs were observed of acute agranulocytosis, with ulcero-necrotical processes in the throat, or other places.

As therapeutic treatment was tried extract of liver, iron in large doses, a course of arsenic, local X-ray irradiation against the splenic region, and blood transfusion (April 9), — all without definite effect on the disease. Salicylic acid alleviated the articular pain only inconsiderably. The pain in the splenic region gradually necessitated morphine in order to be relieved.

<sup>1</sup> All blood counts and bone marrow punctures in this paper have been carried out and described by A. Schrupf.

Per cent	Jan. 24 1942	April 15 1942	April 21 1942	Nov. 17 1942	Nov. 11 1942
Myeloblasts .....	0.8	S P L E N E C T O M Y	1.3	1	1
Promyelocytes .....	0.1		1.3	4	2
Myelocytes .....	35		5	13	14
Metamyelocytes .....	23		22	13	22
Rod forms .....	7.5		21	16	19
Segmented forms .....	0.5		36	13	12
Lymphocytes .....	10		7	18	24
Monocytes .....	0.5		1.8	1	0
Promegaloblasts .....	0		1	1	2
Basophil and other normo- blasts.....	22.6		3	18	3
Plasma and reticulum cells ....	0		0.3	2	0
Megakaryocytes .....	0		0.3	0	1

Fig. 3. Case 1. Bone marrow punctures, before and after splenectomy.

As her condition became alarming, we decided to give the patient the chance we saw in extirpation of the spleen. *The hyperplastic, slightly injured bone marrow indicated that the prognosis might be good if the intervention was successful.*

On April 15, 1942 splenectomy was performed (surgeon-in-chief Gustav Ræder, Porsgrunn).

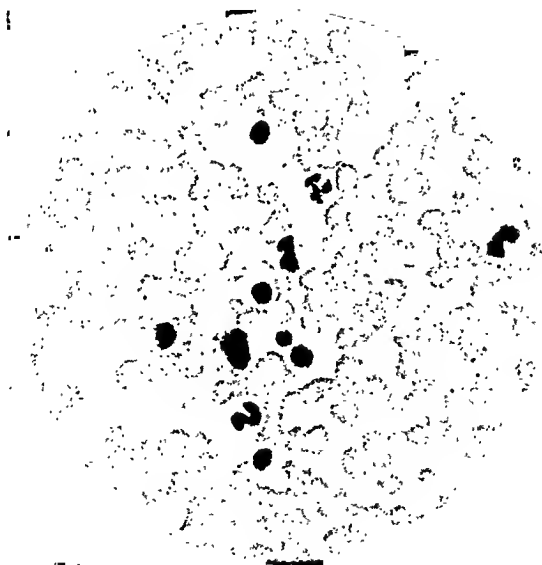
*The spleen weighed 1750 grams. Macroscopically nothing of importance, no infarcts. The microscopy showed slight increase in the number of reticulum cells. The sinus contained, besides lymphocytes, a few plasma cells, and in one place a few neutrophil granulocytes, »cell forms which seem to speak for a chronic state of irritation (chronical splenitis?)». The composition of the cells otherwise normal. The capsule and the sinus walls thickened. Reidar Eker, M. D. concludes: »The findings are only slightly characteristic, and do not tally either with »stasis spleen«, »cirrhosis spleen« or any specific disease». *Diagnosis:* Spleen with fibrosis in the sinus.*

The reaction upon the intervention was striking. The patient recovered amazingly rapidly, became afebrile from the second day after the operation, and the furunculosis disappeared. A marked *leucocytosis* and *thrombocytosis* developed. *The maturation arrest was immediately relieved.* Profuse quantities of segmented forms appeared. The anemia lasted a short time, then disappeared (figs. 1, 2, 3).

Control 7 and 19 months after the operation showed excellent general condition. She had regained her normal weight, and was in full work on a farm. The blood picture was normal, except for some shift to the left (figs. 1, 2, 3, 5). The articular pain disappeared some months after the operation, and did not recur. The function of the liver also—which apparently had been



*Fig. 4. Case 1. Bone marrow puncture on March 21, 1942. The photograph shows that uniformly the red blood cells are poorly saturated with pigment. The myelopoiesis is lively, with a great many myelocytes and metamyelocytes. Segmented forms are not seen. Enlargement  $\times 540$ .*



*Fig. 5. Case 1. Bone marrow puncture on November 17, 1942. The myelopoiesis plays a less prominent part than before the splenectomy. Segmented forms are also seen, and the red blood cells are much better saturated with pigment. Enlargement  $\times 540$ .*

affected, as Takata-Ara's reaction was positive 8 months after the splenectomy — seemed to have improved, as this reaction was negative on control 11 months afterwards.

*Summary:* A woman, 30 years of age, — in whose immediate family there are several persons with rheumatic joint affection, — on admission into the hospital in January 1942, presented a chronic polyarthritis, a considerable splenomegalia, leucopenia with granulocytopenia, anemia, and thrombocytopenia.

The articular lesion began three and a half years earlier in association with an unspecific inflammation of the jaw; enlargement of the spleen, and the changes in the blood, except for the thrombocytopenia, were observed at the same time. Sulfanilamide, but never amidopyrine, had been used. The bone marrow was hyperplastic with maturation arrest in the granulocytopoiesis, after the metamyelocyte phase. No general hypertrophy of the lymphatic glands, or skin pigmentations. Considerable loss of weight in recent years, and gradually declining general condition with secondary infections.

As the therapeutic treatment instituted did not produce any noticeable change in the blood findings during observation for three months, and the general condition became constantly worse, a *splenectomy* was performed. The patient recovered rapidly, the pain in the joints disappeared, the blood picture returned towards the normal, and the recovery persists 19 months after the splenectomy.

#### *Diagnosis and differential diagnosis.*

In this case occurs the triad which forms the S. F. Among inconstant symptoms belonging to the syndrome is found thrombocytopenia, and presumably a slight affection of the liver, while general swelling of the lymphatic glands, pigmentation of the skin and urobilinuria are lacking. Clinically, and from the histological examination of the spleen there are no data in support of any specific disease, as leucemia, for example, or Gaucher's disease; »nothing specific is found», according to the general finding in S.F.

Chronic hereditary haemolytic jaundice can be excluded: jaundice and anemic crises have never occurred; serum colour, and size and shape of the erythrocytes were found to be normal. Osmotic

resistance of the red blood cells was, unfortunately, not performed before after the splenectomy, but previous experiences have shown that a lowered resistance usually persists after splenectomy. In this case the osmotic resistance was found to be normal after the operation.

Judging the case there is no data in support of essential thrombocytopenia. A pannmyelophthisis would hardly give such a hyperplastic bone marrow as in this case.

It may be difficult to exclude the so-called *phlebostenosis splenica* (stricture of the splenic vein), when splenomegalia and blood changes are found as in S. F., hematemesis or melena are lacking, and esophageal varices have not been demonstrated. Even by direct inspection during laparotomy it may be difficult to make an exact diagnosis, because the whole portal vein system is rarely surveyable, and even with good survey no demonstrable cause for the enlargement of the spleen is found [Aubert (3), Ekelund (17)]. The histological examination of the spleen may give the diagnosis [stasis of the spleen, with fibrosis. Brandberg (8), Rö (56)]. However, this histological diagnosis is not specific.

In case 1 there were no clinical signs of stricture of the splenic vein, the histological picture showed no stasis of the spleen, and during the laparotomy nothing abnormal was found in the splenic vein. Thus no certain data in support of a *phlebostenosis splenica* existed, even if the polyarthritis is looked upon as a separate disease and is disregarded.

In 1942 the Swede Selander (61) describes a syndrome, which the Americans Wiseman and Doan (76) in 1939 were the first to point out viz. splenomegalia — myeloid hyperplasia of the bone marrow with qualitatively normal cells — and leucopenia with peripheral granulocytopenia. Their characteristic feature was great discrepancy between the number of neutrophil granulocytes in the peripheral blood and in the spleen (after splenectomy). There was marked phagocytosis of granulocytes in the spleen. They regarded the hypertrophy as compensatory, and the spleen as the leucocyte-destroying organ.

A picture of disease like the above should be kept in mind and taken into consideration. The presence of infectious factors speak against this diagnosis. Histological examination of the spleen will secure the diagnosis viz. increased phagocytosis of granulocytes.



In case 1 an inconsiderable phagocytosis was found in the spleen, moreover occurred here a definite infectious factor.

The frequent occurrence of rheumatic infection in the family of this patient, and at the same time information about one of her sisters having enlargement of the spleen, gave rise to a closer examination of this sister.

*Case 2*<sup>1</sup>: M. H., 36 years of age. The onset of the present disease was in January 1927 with angina, associated with rather acutely occurring pain in various joints, and increased temperature. Stayed in bed for 7 weeks. The subsequent course has been characterized by frequent periods of relapse, and until 1941 a slow progression of the articular lesion resulting in deformity and invalidity in such a way that she has been confined to bed for the last two years. From 1928 to 1939 a total of eight stays in hospital for her *polyarthritis*, which has shown stationary tendency since 1941.

In 1935 *anemia* was demonstrated. (Hemoglobin: 60 per cent). Two years later *leucopenia with granulocytopenia* was discovered (700 white blood cells per cubic millimetre, 9 per cent segmented forms), *thrombocytopenia*: (80,000) and *hepato-splenomegalia*, both the latter palpable down to the umbilicus. At the same time icterus was found (serum colour 40), and petechiae of the skin. The enlargement of the liver quickly regressed, together with the icterus and the skin hemorrhages. The thrombocytopenia also disappeared. During the last years the anemia has varied somewhat. (60 to 90 per cent). The number of white blood cells has never been higher than 2700 per cubic millimetre. It is of special interest that the size of the spleen has varied somewhat during these years. The patient indicates pain in the splenic region in connexion with the exacerbations of the polyarthritis, and at the same time the physician in charge found an increase in the size of the spleen.

Her general condition during all these years has been relatively good in spite of a constantly increasing loss of weight, about 20 kilos from 1927.. The sedimentation rate has always been considerably increased. For medication have been used besides salicylic acid, during a short time amidopyrine and sulfanilamide, as also liver extract and iron. Hemorrhages from the skin or the digestive tract have never been observed.

*Physical examination, December 8, 1942* (most important findings): Thin. Pulse 88, regular. Blood pressure 140/110. No general hypertrophy of the lymphatic glands, and no skin pigmentations. The liver is palpable two fingerbreadths below the costal arch, consistency normal. *The spleen*: Dulness in front of the median clavicular line. Not definitely palpable. Roentgenological examination of the splenic region shows a slightly enlarged splenic shadow.

<sup>1</sup> In a subsequent paper Ö. Ytrelus from the University Clinic Department A. of Internal Medicine, where the patient was under treatment in the course of the years 1937—1939, will refer this case in connexion with two others.

Leucocytes .....	2075		Erythrocytes.....	4.16 mill.
Myelocytes .....	0	%	Hemoglobin ....	76 %
Young forms .....	6.5	"	Colour index.....	0.92
Rod forms .....	13.5	"	Platelets .....	276.250
Segmented forms .....	10.5	"	Sedimentation rate	38 mm
Eosinophiles .....	23.5	"	Serum colour ....	3.5
Basophiles .....	1.5	"	Osmotic resistance	beginning: 0.46
				Total: 0.36
Lymphocytes .....	43	"	Bleeding time ....	2.5 min.
Monocytes .....	1.5	"	Clotting time ....	1.5 min.

Fig. 6. Case 2. Blood examinations December 1942.

*The joints.* The metacarpo-phalangeal joints and finger joints are swollen, deformed, semiflexed, with ulnar deviation, and almost ankylosed. The carpal joints are swollen, ankylosed, volarly flexed. Roentgenological examination of hands and carpal joints demonstrates marked polyarthritic changes. The knee joints are highly fusiformly swollen and deformed. The calves of the legs form a 90 degree angle with the thighs. The flexibility is about 10°. Slightly polyarthritic changes in elbow- hip- and too joints. No pain in the joints, no sign of «active» process.

*Laboratory examinations.* Urine: pyuria, otherwise physiological. Reticulocytes 2.6 per cent. Meinicke II negative. Uric acid in the blood: 9 milligram per cent. Takata-Ara's test: positive. Glucose test normal. Galactose test: no excretion of sugar in the urine after six and eleven hours.

Otherwise reference is made to figs. 6 and 7. *Leucopenia* with 10.5 per cent segmented forms in the peripheral blood should be specially noted.

Myeloblasts .....	1 %
Promyelocytes .....	4 "
Myelocytes .....	9 "
Metamyelocytes.....	19 "
Rod forms .....	14 "
Segmented forms .....	5 "
Lymphocytes .....	17 "
Monocytes .....	1 "
Promegaloblasts .....	1 "
Basophil and other normoblasts .....	29 "
Plasma and reticulum cells .....	0 "
Megakaryocytes.....	0 "

Fig. 7. Case 2. Bone marrow puncture December 1942.

*Diagnosis and differential diagnosis.*

This patient also shows the triad viz. chronic rheumatic polyarthritis, splenomegalia and leucopenia with granulocytopenia. Otherwise slight hepatomegalia, anemia and a considerable loss of weight year by year, all characteristic of a S. F. There are no data whatever in support of leucemia, haemolytic jaundice, thrombocytopenia or phlebosclerosis splenica, neither clinically nor by laboratory examinations.

During her previous hospitalization Gaucher's disease has been taken into consideration, but definite data were never found, especially not Gaucher cells in the bone marrow puncture. A hypertrophy of the spleen with so great a regression does not occur in Gaucher's disease.

The hypertrophy of the liver in 1937 may have been an acute hepatitis, and at that time a S. F. did not come into consideration, therefore. The slightly enlarged liver found at the last control however, should probably be included among the inconstant symptoms of S. F., as it cannot be explained in any other way.

The third sister suffering from polyarthritis has also been examined with a view to S. F. (K. S. — 28 years of age). Except for slight polyarthritic changes in the finger joints, no hypertrophy of the liver or spleen, no leucopenia (6800) or anemia (Hb. 104 per cent), and a normal number of platelets (267,000) were found. *S. F., therefore, was not present.*

No opportunity has been offered of examining the remaining members of the family suffering from polyarthritis.

### Discussion.

**The Granulocytopenia.** The most striking finding in case 1 is the granulocytopenia (g). It may be of interest, therefore, to discuss the relation between this and the remaining symptoms.

Lichtenstein (36) has distinguished between acute and chronic malignant g. Cases which at the same time have anemia and thrombocytopenia are termed »combined» forms by von Bonsdorff (74). Rohr (55) compiles the following etiologic classification of g.:

- a. anaphylactic forms.
- b. toxic forms (chemical and infectious).

c. hypersplenic forms (in connexion with a hepato-splenic syndrome).

d. «accompanying granulocytopenia» (accompanying symptom in certain diseases, as for example leucemia).

The most plausible is, in case 1, to classify the g. as a «combined» type, of toxic or hypersplenic origin, or possibly a combination of both.

Many authors claim that an *infectious-toxic* factor often may be traced in connexion with a malignant g., acute or chronic. Thus von Bonsdorff (74) in his paper on g. reports the infectious factor as one of the causes. He emphasizes, however, that some authors look upon the infection as secondary in connexion with the g.

Rohr (53) points out the occurrence of g. after a number of previous diseases, such as polyarthritis, and emphasizes that particularly *chronic* infections cause a general decrease in the resistance of the organism, which is necessary for the g. to occur. Doxiades (15) mentions examples of infection of rheumatic character and a protracted, undulant course of leucopenia with neutropenia.

Stachelin (66) has seen chronic g. in chronic arthritis, and supposes that an infection in particularly disposed individuals may start a malignant g. He points out that sepsis and g. frequently concur; it is an open question whether the present sepsis has brought about a particularly severe injury of the bone marrow, or whether the changes in the blood have made possible invasion of micro-organisms. «The result will be the same for the patient, however».

Further it may be mentioned that Sabrazes & Saric (57) have demonstrated by animal experiments that streptococcus viridans may give agranulocytosis.

Nordenson (44) in 1936 refers ten cases of g., six of which had polyarthritis (one case also splenomegalia). In two cases occurred a chronic g. — Sundelin (68) reports leucopenia-granulocytopenia in connexion with septic infection of the tonsils, the oral cavity, and the accessory sinuses of the nose, together with symptoms of arthritis. — Similar observations of infection and g. have been recorded by Y. Ustvedt (72) and Linneberg (37).

Therefore, one must presume that infection and g. may be correlated, and most likely in such a way that in *some* of the cases the g. *originates from direct infectious-toxic effect on the bone marrow*. With the infection as the primary factor it may be presumed that the organism *in particularly disposed individuals* is in a stage of «granulocytopenic preparedness», only waiting for a releasing factor (the infection).

**The Hypertrophy of the Spleen.** (h. s.) The next question which arises, namely the relation between *infection* and *hypertrophy of the spleen* is discussed by Brandberg (8) in his paper from 1935 in the chapter on »the chronic infectious hypertrophy of the spleen». Besides many specific diseases (malaria, tuberculosis, endocarditis lenta, lues), he also includes in this group sepsis of chronic type. According to Brandberg (8) h.s. in this latter disease has been reported many times in the literature. In this latter group he also includes S. F.

It is worth noticing that h.s. and g. in case 1 is observed *before* the symptoms from the joints started. As far as one has been able to find, a similar observation has not been done previously. According to this it may appear as if S. F. occurs in particularly disposed individuals with g. and h. s. *when a secondary polyarthritis is present!*

However, the primary factor in the history of disease is an infection, the infection of the jaw. H. s. may be *released* through this infection, as also the leucopenia, — possibly (also) via the spleen. The infection must be assumed to be arthrogenous, but in the latent period before the articular symptoms occur, the changes in the blood and the h. s. appear.

If this explanation is accepted the case may be classified under the present conception of S. F., as caused by an infection. *The reported observation, however, is of interest, and should urge future observers of the syndrome especially to note the order in which the splenomegalia, the changes in the blood, and the polyarthritis begin. —*

Changes in the size of the spleen, — as in case 2, — are reported by Breu and Fleischhacker (9) in S. F. They observed an increase in the size in acute stages of the disease, a decrease in »quiet» periods, in accordance with this patient's history of disease. Similar changes in the size of the spleen are known from Still's disease, which, as mentioned, is regarded as closely related to S. F. [Neugebauer (43), Hajkis (25)].

**The »aplastic» Blood Picture.** In the literature the peripheral blood picture of S. F. is reported to adopt a more »aplastic» appearance, as the disease progresses. Case 2 shows deviation from this — the anemia has varied, the thrombocytopenia has disappeared. The most constant finding has been the leucopenia, with values never above 2700 white blood cells per cubic millimetre.

The variation of the spleen and blood findings in case 2 may be

explained as changes in the intensity of the disease. The »quiet» stage, at which the patient had arrived in recent years explains the regression in the findings.

**The Familial Occurrence.** Further, the familial occurrence of S.F. in these cases is worth noticing. This points towards the presence of an *endogenous-constitutional factor*, such as Edström (16) has pointed out regarding the occurrence of granulocytopenia. A familial occurrence of S. F., as described here, has not been reported previously, however. —

Which rôle does the spleen play in this picture of disease?

Case 1 illustrates the presence of a maturation arrest of the bone marrow, which virtually is removed with the spleen. Do we have definite data to support the conception of the spleen having a regulating influence on the bone marrow? Does the spleen inhibit the entire haematopoiesis, or part of it, resulting in anemia, leucopenia and thrombocytopenia?

Bock and Frenzel (6) (1938) assert having proved such an inhibition in experiments on rabbits. They conducted the blood from the spleen outside the liver directly into the main circulation of the blood, and found the typical blood changes.

The inhibiting influence is especially ascribed to the splenic reticular cells, as these have allegedly been found to be proliferating.

Troland and Lee (69) in 1938 extracted from the spleen of three individuals suffering from thrombocytopenic purpura a substance, which injected on rabbits caused a marked thrombocytopenia. Pohle and Meyer (50) one year later did not succeed in reproducing these experiments.

Engelbreth-Holm (18) strongly advocates the conception of the blood changes being caused by an arrest of the maturation, or a migration of blood cells from the bone marrow (maturation arrest or blocked circulation). van Buchem (73) in his paper on the influence of the spleen on the erythropoiesis denies the presence of any inhibiting influence of the spleen on the bone marrow.

It will be too lengthy to mention all the authors (13, 20, 29, 30, 41, 54, 59, 75) who support or oppose a bone marrow inhibition originating in the spleen. We will content ourselves with quoting Lauda (34): »Little is definite in the pathology of the spleen; a multitude of case histories, theories and hypotheses exist». He asserts that as yet an inhibition of the bone marrow from the spleen may only be assumed.

Nordenson (47) opines that due to all the uncertainty in the

pathology of the spleen until further one should talk about a «*dysfunction* of the spleen», and avoid the expression «inhibition».

Such a «*dysfunction*» appears to be present in S. F. The results of splenectomy in S. F. support this conception, also in case 1, because the «*dysfunction*» disappeared after removal of the spleen.

As previously mentioned a *direct* infectious-toxic injury of the bone marrow also may be assumed. Definite conclusions regarding the pathogenesis of the blood changes in S. F. at the present stage can hardly be arrived at. The influence on the bone marrow may proceed directly or via the spleen, or both ways.

**The Use of Sulfanilamide.** May the rather large quantity of sulfanilamide (s.) used in case, 1, have anything to do with the blood changes, possibly have contributed to the release of these changes?

The s. belongs to the «*haemotoxic*» substances, with occurrence of anemia, granulocytopenia and thrombocytopenia. The releasing mechanism is presumed to be partly toxic [Shecket and Price (63)], partly anaphylactic [Majoor (38)]. No agreement has been reached on this point.

Plum and Thomsen (49) are among the many investigators (1, 4, 5, 22, 31, 32, 42, 46, 60, 62, 71) who have pursued the s.-agranulocytosis. In contrast to the majority, they maintain that the dose does not have to be particularly large (less than 20 grams), and that the latent period may be less than four weeks.

This concerns the *acute* occurrence of granulocytopenia after the use of s. A particularly *chronic* course has not been described, as far as one has been able to find. Theoretically such a chronic type cannot be excluded. Nordenson and Roden (48) lately have reported a granulocytopenia of chronic type after the use of other therapeutic agents:

The case refers to a woman, 50 years of age, who after amidopyrine medication and roentgen irradiation for a chronic polyarthritis, developed a chronic granulocytopenia observed through four years. Besides this she also showed thrombocytopenia, anemia, splenomegalia, a hyperplastic bone marrow, with maturation arrest, and gradually declining general condition. After the splenectomy the blood picture became normal, and she regained perfect health. The authors regard the use of amidopyrine and the roentgen irradiation as the releasing factor.

From a symptomatic point of view this case is a S. F. The authors emphasize that the distinction is dependent on the assumed therapeutical etiological factor.

The angina present in case 1 during the second hospitalization in 1938 might very well have been an angina agranulocytotica, to judge from the description and the haematological findings. The fact of its being «cured» after 66 grams of s. does not disprove the diagnosis; similar recovery has been observed by Bralme (7) and Hafstrom (7). The s. could hardly have been any *releasing* cause of the blood changes. The small dose of four to six grams before the onset of the angina can hardly be conceived to have played this rôle.

No definite data exist to prove whether the comparatively regular consumption of s. in the following years may have influenced the blood picture. To find out, if possible, whether the blood forming organs reacted to s. with inhibition of the granulocytopenesis, a «sulfanilamide test» was performed both in case 1 and 2, similar to the amidopyrine tests performed on suspicion of an amidopyrine agranulocytosis (a total dosage of four grams within 24 hours in single doses of one gram). The tests *did not give positive result*. In case 1, however, the test was done after the splenectomy, which possibly may have reduced its value.

### *The Treatment.*

There is not much to choose between. For chronic leucopenia with g. it cannot be expected to obtain any appreciable effect with the usual media applied for malignant g. (nucleic acid, liver extract, etc.). The anemia, as well as the thrombocytopenia, are only slightly or not at all influenced. If an acute attack of agranulocytosis should occur, general treatment should be tried; Fleischhacker and Lachnit (21) especially recommend blood transfusions. No definite effect of treatment with splenic extract exists at present [Savolin (58), Haenlein and Schliphacke (24), Troland and Lee (69), Pohle and Meyer (50), Marberg and Wiles (39)]. Furthermore, the foundation for such a therapy still is too uncertain.

What is left to do is to remove the spleen. Should this be done? Even if this organ may be removed with safety, however, we do not know all the functions of the spleen, neither in healthy nor in pathological condition. Among other things a large part of the reticulo-endothelial cells of the organism is removed, cells which are regarded as a defence against infections [Landa (34), Kreyberg (33),



and others]. Theoretically a splenectomy should be indicated, if there is reason to believe that the infection »survives» in the spleen, but is »extinguished» in other parts of the organism, in such a way that the spleen may be made responsible for the further development of the disease [Brandberg (8)].

To decide this in practice must often be pure conjecture. Previously splenectomy in S. F. has been done four times, as far as we have been able to find [Hanrahan and Miller (26), Craven jr. (11), Trolle and Trolle (70), Gyntelberg (23)]. In two cases good effect was observed in the blood picture and the joint affections, in the third case good effect immediately after the operation, somewhat later followed by slight joint affections. In the fourth case the patient died of sepsis shortly after the operation.

Pondering for and against splenectomy, the conclusion arrived at is that each separate case should be dealt with individually. The bone marrow picture must be examined with much care. Norden-son (47) points out that the more developmental stages of the myeloid cells are represented in the bone marrow, that is to say, the less injured the bone marrow is, the better chance the patient has by a splenectomy. Further, chronicity in g. is regarded as connected with a certain degree of benignity [von Bonsdorff (74)]. Continual decrease of the general condition, exacerbation of the blood picture, frequent weakening secondary infections, constant attacks of polyarthritis with aggravation of this, and possibly also local pain in the enlarged spleen, separately or combined, speak for a splenectomy being attempted.

In case 1, referred above, the condition was regarded as being so precarious that the patient was permitted to take the chance which lay in a splenectomy, and with good result. In case 2, on the other hand, we did not advise operation, as the spleen, liver and blood findings showed considerable improvement with the years, and the polyarthritis seemed to have become stationary.

### Conclusions.

The conclusions drawn from the above mentioned two cases will be the following:

1. In certain predisposed individuals suffering from polyarthri-

tis, the picture of disease may show a granulocytopenia and hypertrophy of the spleen, i.e. a syndroma Felty occurs (S. F.).

2. The above mentioned *familial* occurrence of the syndrome confirms that the disposition is closely attached to endogenous, constitutional factors.

3. Probably malfunction of the spleen is a factor, which plays a rôle, — possibly the main rôle — in the pathogenesis of the changes in the blood under the conditions mentioned. This hypothesis is supported by the fact that after removal of the spleen in case 1, a complete clinical recovery was obtained.

4. A direct infectious-toxic injury of the bone marrow as a releasing factor for the blood changes cannot be disregarded. Case 1 and 2 do not prove anything definite in this respect.

5. In the few cases in the literature, in which splenectomy has been performed in S. F., the results have partly been good, resulting in clinical recovery. The favourable result of splenectomy in our case 1 supports the standpoint that one should not be too reserved, in the presence of this syndrome, with regard to extirpation of the spleen. However, the haematological picture should be carefully studied before an operation is decided on.

6. Based on own observations, it is discussed, whether the present conception of S. F. is correct, as a general infection of the organism of rheumatic character, followed by hypertrophy of the spleen and blood changes, — or if the last two factors are independent of the *rheumatic* infection. No definite conclusions regarding this may be drawn from case 1. *This important and interesting question still awaits its complete elucidation.*

### Summary.

One case of syndroma Felty in a female, 30 years of age, is recorded. The patient presented the typical triad of: 1. chronic polyarthritis, 2. leucopenia with granulocytopenia, 3. enlarged spleen. One sister of this patient presented a similar clinical syndrome. After removal of the spleen the first patient described above recovered completely and is in full work on a farm.

From the data submitted it is concluded that granulocytopenia in certain predisposed individuals with polyarthritis may present

the clinical picture of a syndroma Felty. The disposition is closely attached to an endogenous-constitutional factor, which is concluded from the occurrence of syndroma Felty in two sisters.

Even if a direct affection of the bone marrow is not to be excluded a malfunction of the spleen is a factor of great importance to the changes in the leucopoiesis (granulocytopenia) and the occurrence of the actual syndrome. This is supported by the fact of the complete recovery which followed when this factor was eliminated through removal of the spleen.

### References.

1. Allen, J. G. and Short, C. L.: Year Book Gen. Med. 1938: 443. —
2. Allesandrini, P.: La Presse medic. 1934: 42: 1190. — 3. Aubert, A.: Nord. Med. 1941: IV: 3653. — 4. Bang, O.: Ugeskrift f. Læger 1942: 104: 138. —
5. Berg, S. and Holzman, M.: J. A. M. A. 1938: 110: 370. — 6. Bock, E. H. and Frenzel, B.: Klin. Woch. 1938: 17: 1315. — 7. Brahme, L. and Hafström, T.: Nord. Med. 1944: 21: 276. — 8. Brandberg, R.: Acta Chir. Scand. 1935: suppl. 40. — 9. Bren and Fleischhacker: Wiener klin. Woch. 1938: 51: 1081. — 10. Chauffard and Ramond: Revue de Medicine 1896: 16: 345. — 11. Craven jr., Erle B.: J. A. M. A. 1934: 102: 823. — 12. Curtis and Pollard: Ann. Int. Med. 1940: 13: 2265 (refer also no. 23). — 13. Custer and Krumbhaar: A. J. Med. Sciences 1935: 189: 620. — 14. Dawson: Nelson New Loose Leaf Med. v. 625. — 15. Doxiades, Th.: Klin. Woch. 1932: I: 419. — 16. Edström, G.: Nord. Med. 1941: II: 1873. — 17. Ekelund, C.: Nord. Med. 1943: 17: 434. — 18. Engelbreth-Holm, J.: Bibl. f. Læger 1937: 129: 17. — 19. Felty, A.R.: Bull. John Hopkins Hosp. 1924: 35: 16. — 20. Fitz-Hugh and Krumbhaar: A. J. Med. Sciences 1932: 183: 104. — 21. Fleischhacker and Lachnit: Wiener klin. Woch. 1940: 53: 189. — 22. Gayus, Geen-Armytage and Baker: Brit. Med. J. 1939: 560. —
23. Gyntelberg, I.: Nord. Med. 1942: 13: 927. — 24. Haenlein, E. and Schlipphake, E.: Klin. Woch. 1935: 14: 79. — 25. Hajkis, M.: Norsk Mag. f. Lægevid. 1936: 97: 173. — 26. Hanrahan and Miller: J. A. M. A. 1932: 99: 1247. — 27. Harrison, F.: A. J. Med. Sciences 1930: 179: 208. — 28. Hench, P. S.: see number 64. — 29. Holten, C.: Nord. Med. 1939: IV. 3258. — 30. Holten, C. and Munkholm, I.: Nord. Med. 1940: I: 332. — 31. Johnstone, F. D.: Lancet 1938: 235: 1044. — 32. Kracke, R.: J. A. M. A. 1938: 111: 1255. — 33. Kreyberg, L.: Norsk Mag. f. Lægevid. 1933: 96: 1365. — 34. Lauda, E.: Klin. Woch. 1937: 16: 977. — 35. Leichtentritt: Erg. Inn. Med. 1930: 37: 68. — 36. Lichtenstein, A.: Acta Med. Scand. 1932: suppl. 49. — 37. Linneberg, L.: Norsk Mag. f. Lægevid. 1935: 96: 31. — 38. Majoor, C. L.: Nord. Med. 1939: III: 2300. —
39. Marberg and Wiles: J. A. M. A. 1937: 109: 1965. — 40. Mc. Crae: J. A. M. A. 1904: 42: 1. — 41. Meulengracht: Nord. Med. 1941: III:

2309. — 42. Myhre, H.: *Acta Med. Scand.* 1939: 99: 614. — 43. Neugebauer: *Wiener Arch. Inn. Med.* 1937: 31: 231. — 44. Nordenson, N. G.: *Svenska Läkartidn.* 1936: 33: 1145. — 45. Nordenson, N. G.: *Nord. Med.* 1940: II: 834. — 46. Nordenson, N. G.: *Nord. Med.* 1940: IV: 1899. — 47. Nordenson, N. G.: *Svenska Läkartidn.* 1941: 38: 2785. — 48. Nordenson, N. G. and Röden, S.: *Acta Chir. Scand.* 1941: vol. 84: 519. — 49. Plum, P. and Thomsen, S.: *Nord. Med.* 1940: II: 1056. — 50. Pohle and Meyer: *J. Clin. Invest.* 1939: 18: 537. — 51. Pollitzer, H.: *Med. Klin.* 1914: 10: 1511 (refer also no. 65). — 52. Price and Schoenfeld: *Ann. Int. Med.* 1934: 1230 (refer also no. 9). — 53. Rohr, K.: *Münchener Med. Woch.* 1935: 82: 460. — 54. Rohr, K.: *Helvetia Med. Acta* 1935: 1: 713. — 55. Rohr, K.: *Fol. Haematol.* 1936: 55: 305. — 56. Rö, J.: *Norsk Mag. f. Lægevid.* 1936: 97: 603. — 57. Sabrazes, J. and Saric, R.: *N. M. Tidsskr.* 1936: I: 650. — 58. Savolin, M.: *Nord. Med.* 1942: 13: 742. — 59. Schousboe, J.: *Nord. Med.* 1939: II: 1980. — 60. Schwartz, Carvin and Koetsky: *J. A. M. A.* 1938: 110: 368. — 61. Selander, P.: *Nord. Med.* 1942: 16: 3565. — 62. Shaw, C. C.: *N. M. Tidsskr.* 1938: II: 1260. — 63. Sheckett, H. A. and Price, A. E.: *J. A. M. A.* 1939: 112: 823. — 64. Singer, A.: *J. A. M. A.* 1933: 101: 2078. — 65. Singer, A. and Levy: *Arch. Int. Med.* 1936: 57: 576. — 66. Staehelin, R.: *Münchener Med. Woch.* 1938: 85: 1419. — 67. Still: *Medico-chir. transact.* 1897: 80: 47. — 68. Sundelin, F.: *N. M. Tidsskr.* 1937: II: 2034. — 69. Troland, C. E. and Lee, C. F.: *J. A. M. A.* 1938: 111: 221. — 70. Trolle and Trolle: *Nord. Med.* 1943: 18: 757. — 71. Tyson, T. Lloyd: *Nelson New Loose Leaf Med.*: v. VIII: 12. — 72. Ustvedt, Y.: *Forh. Det norske med. Selskab* 1935: 169. — 73. van Buchem: *Acta Med. Scand.* 1938: 97: 596. — 74. von Bonsdorff: *Acta Med. Scand.* 1937: 91: 555. — 75. Wahlquist, S.: *Acta Med. Scand.* 1934: 39: 184. — 76. Wiseman, D. K. and Doan, C. A.: *J. Clin. Invest.* 1939: 18: 473.

---

Ask-Upmark, E.: *Acta Med. Scand. suppl.* 78: 226. — Embleton, D.: *Brit. med. J.* 1936: II: 1258. — Eppinger, H.: *Die Hepato-lienalen Erkrankungen.* 1920. — Frölich, Th.: *N. M. Tidsskr.* 1930: II: 337. — Geissler, H.: *Nord. Med.* 1941: I: 784. — Hirschfeldt, H.: *Die Erkrankungen der Milz.* — 1920. — Jervell, A.: *Tidsskr. Den norske Lægefor.* 1938: 493. — Johannesen, A.: *Norsk Mag. f. Lægevid.* 1899: 12. — Lorenz, E.: *N. M. Tidsskr.* 1938: I: 312. — Meuther, Moore, Stewert and Broun: *J. A. M. A.* 1941: 116: 2255. — Mowinckel, K.: *Ugeskr. f. Læger* 1941: 103: 819. — Raynaud, Imbert and d'Eshougues: *Le Sang* 1938: 12: 327. — Stodtmeister and Buchmann: *Klin. Woch.* 1941: 20: 329. — Stodtmeister and Buchmann: *Klin. Woch.* 1941: 20: 419. — Strasser, U.: *N. M. Tidsskr.* 1932: 894. — Sundt, H.: *Acta Orthopaed. Scand.* 1936: v. 7: 205. — Troell, A.: *N. M. Tidsskr.* 1932: 578. — Wagner, H. K.: *Klin. Woch.* 1941: 20: 574. — Zeiner-Henriksen: *Forh. Det norske med. Selskab.* Oslo 1934: 78. — Zetterquist, A.: *Acta Med. Scand.* 1927: 67: 172.

---

Aus der I. medizinischen Klinik der Universität Helsinki; Vorstand  
Prof. Arvo Vesa.

## Klinische Untersuchungen über die Polyzythämie. II.

*Polycythaemia essentialis.*

Von

MARTTI HIRVONEN.

(Bei der Redaktion am 11. September 1944 eingegangen).

Wie ich im ersten Teil meiner Arbeit erwähnte, war Vaquez der erste, der die Polyzythämie ohne bekannte Ursache feststellte und 1892 in der Literatur beschrieb. Die *Polycythaemia essentialis* oder Vaquezsche Krankheit ist recht ungewöhnlich, obwohl nicht zu den grössten Seltenheiten auf dem Gebiet der Krankheit gehört. So fand Lucas, der zwanzig Jahre nach der Veröffentlichung von Vaquez alle bis dahin mitgeteilten sicheren Fälle von *Polycythaemia essentialis* sammelte, ihrer 123. Die Krankheit entwickelt sich langsam, und ihr zentralstes Symptom ist, wie aus dem Namen angibt, eine aus unbekannter Ursache erfolgende Abnahme der Erythrozytenzahl und auch der ganzen Blutmenge.

Obgleich die Ätiologie der Krankheit, wie gesagt, immer unbekannt ist, ist konstatiert worden, dass mehrere Faktoren ihrer Entstehung von Bedeutung sind. So ist die Frequenz der Krankheit bei den verschiedenen Rassen verschieden. Türk beobachtet, dass die Juden häufiger an *Polycythaemia essentialis* erkranken als die Angehörigen der anderen weissen Rassen. Dies wird auch dadurch bewiesen, dass sich unter den von Lucas gemeldeten 123 Fällen von sicherer *Polycythaemia essentialis* 11 Jüdinnen befanden. Da die Rasse nicht in allen Fällen bekannt ist, kann

Zahl der Juden noch grösser gewesen sein. Auch so beliefen sich die Juden auf 9 %. Reznikoff, Foot und Bethca haben einen noch viel höheren Prozentsatz für die Juden festgestellt. Unter den von ihnen gesammelten 134 Fällen waren nämlich 48 % Juden. Dieser Prozentsatz ist ungefähr 4 mal so gross wie der Anteil der Juden überhaupt an der Menge der Patienten in den osteuropäischen Ländern, in denen ihr Material zusammengebracht worden ist. Andererseits hat Fletcher bemerkt, dass die Polycythaemia essentialis unter den farbigen Rassen recht selten vorkommt.

Die an Polycythaemia essentialis leidenden Patienten sind öfter Männer als Frauen. So war das Verhältnis der männlichen zu den weiblichen Patienten in dem Material von Lucas 2: 1. In den 32 Fällen, die Fletcher aus dem Material des John Hopkins Hospital zusammengestellt hat, war dieses Verhältnis noch etwas grösser, nämlich 3.5: 1.

Die Krankheit beginnt im allgemeinen erst in den mittleren Jahren oder wenn der Patient schon alt ist. Indes sind einige wenige bei jungen Personen, ja sogar bei Kindern konstatierte Fälle von Polycythaemia essentialis veröffentlicht worden. Der jüngste von diesen ist der Fall von Stransky und Willenberg, der ein 6 Wochen altes Kind betrifft, bei dem im Alter von 12 Wochen 6.25 Millionen Erythrozyten und 11,200 Leukozyten nachgewiesen wurden. Es kann sich dabei nicht um die symptomatische Polyzythämie der Neugeborenen handeln, denn die Werte stiegen allmählich höher an, und bei der Obduktionen konnten ein stark hyperplastisches rotes Knochenmark, eine grosse Milz und eine Peritonitis, an der das Kind starb, festgestellt werden. Es hatte auch keinen angeborenen Herzfehler, der eine symptomatische Polyzythämie hätte auslösen können. Halbertsma hat ebenfalls eine typische Polycythaemia essentialis bei einem sechsjährigen Knaben veröffentlicht. Bei 17—18jährigen ist Polycythaemia essentialis u. a. von Chace, Sandesky, Reissmann und Hann konstatiert und veröffentlicht worden, aber in diesen Fällen ist nicht mit Sicherheit nachgewiesen, dass es sich nicht um eine auf Grund eines angeborenen Herzfehlers entwickelte Polycythaemia symptomatica gehandelt haben könnte.

Die Polycythaemia essentialis kommt äusserst selten auch in hereditärer oder familiärer Form vor. Diese unterscheidet sich in einiger Hinsicht von der eigentlichen Polycythaemia essentialis.

So beginnt die hereditäre Form im allgemeinen schon im Kindesalter oder wenigstens in jungen Jahren, und die Krankheit ist bedeutend gutartiger als die eigentliche Polycythaemia essentialis. Die hereditäre Form vererbt sich dominant. Sie verursacht nur selten subjektive Beschwerden. Es besteht bei ihr im allgemeinen keine Leukozytose, und auch Jugendformen der Blutkörperchen treten nicht im Blute auf. Manche Forscher, wie Harrop und Wintröbe, sehen in der Krankheit eine ganz andere als die eigentliche Polycythaemia essentialis. Die bekanntesten Familien, in denen hereditäre Polyzythämie konstatiert worden ist, sind von Engelking und Wieland veröffentlicht. Bei der eigentlichen Polycythaemia essentialis sind dagegen keine hereditären Eigenschaften festgestellt worden, und man hat nicht gefunden, dass sie sich vererbt.

Wie sich gezeigt hat, verbinden sich mit dem Krankheitsbild der Polycythaemia essentialis bisweilen verschiedenartige endokrine Störungen, und man hat sich gedacht, dass diese Störungen möglicherweise irgendwie mit der Ätiologie der Krankheit zusammenhängen. So meinen Engelking, Naegeli und Hedenius, dass die Polycythaemia essentialis wegen der dann und wann in Verbindung mit der Krankheit auftretenden vielen innersekretorischen Störungen wahrscheinlich von einer Störung des hämatopoetischen System regulierenden endokrinen Gleichgewichts herrühre.

Infantilismus und auch andere Wachstumsstörungen sind besonders im Zusammenhang mit der bei Kindern vorkommenden hereditären Krankheitsform angetroffen worden. Die Menstruationen beginnen, wie beobachtet worden ist, oft in späterem Alter als gewöhnlich. Ferner hat es sich gezeigt, dass die Verfütterung von Schilddrüsenpräparaten manchmal Polyzythämie hervorgerufen hat, obgleich die Befunde meist nicht zutreffend sind. Hinsichtlich der Nebenschilddrüse, der Thymusdrüse und des Pankreas hat sich dagegen kein Zusammenhang mit der Polyzythämie ergeben. Im Zusammenhang mit Erkrankungen der Hypophyse kommt hinwieder Polyzythämie vor, und in diesen Fällen dürfte sie bei der Cushingschen Krankheit am häufigsten sein.

Die Geschlechtsdrüsen haben augenscheinlich etwas mit der Neubildung des Blutes zu tun, da die bei den Männern und den Frauen auftretende Verschiedenheit der Erythrozytenzahl, der

Hämoglobinwerte und auch des Eisengehalts des Serums erst im Pubertätsalter in Erscheinung tritt. Polyzythämie ist auch ab und zu in Verbindung mit gestörter Funktion der Geschlechtsdrüsen gefunden worden. So konstatierte Bauer Polycythaemia essentialis bei Eumehen. Bingel hat auch einen Fall veröffentlicht, in dem ein in einem Ovarium vorhanden gewesener Luteinzellentumor Hypertrichose, Virilismus und Polyzythämie verursacht hatte, Symptome, die sämtlich nach der Exstirpation des Tumors verschwanden.

Wie Günther hervorgehoben hat, dürfte man jedoch den meisten Polyzythämiefällen im Zusammenhang mit innersekretorischen Störungen bei Erkrankungen der Nebennieren begegnen. Er sammelte aus dem Schrifttum 21 Fälle von Nebennierentumor und teilte selbst 2 weitere Fälle mit. In 11 von diesen 23 Fällen war auch das Blutbild untersucht worden, welches zeigte, dass die Erythrozytenzahl in 8 Fällen deutlich erhöht war. In den meisten Fällen wurde auch Leukozytose gefunden.

Auch an manche Gehirnkrankheiten, bei denen wenigstens keine deutlichen innersekretorischen Störungen vorhanden sind, schliesst sich Polyzythämie an. In diesen Fällen hat Günther den Namen zerebrale Polyzythämie in Gebrauch genommen. So beobachteten Model und Wolff bei 12 von 50 an epidemischer Enzephalitis leidenden Patienten Polyzythämie, und Lichtwitz hat 3 Fälle von Parkinsonismus veröffentlicht, in denen Polyzythämie vorlag. Litzner hat Polyzythämie in einem Fall festgestellt, in dem eine Kohlen-  
dunstvergiftung degenerative Veränderungen im Mittelhirn verursacht hatte. Doll und Rotschild hinwieder konstatierten Polyzythämie bei 4 an Chorea progressiva hereditaria Leidenden. Schulkoff und Matthies riefen bei Kaninchen Polyzythämie dadurch hervor, dass sie Kieselgur in die Gegend des vegetativen Gehirnzentrums injizierten.

Der mögliche Anteil der Milz an der Entstehung der Polycythaemia essentialis ist lebhaft diskutiert worden. Anfangs glaubte man, dass in die Milz lokalisierte Tuberkulose einen wichtigen Faktor in der Ätiologie der Polycythaemia essentialis darstelle. Hierbei sprach mit, dass bei der Obduktion mehrere Fälle festgestellt wurden, in denen sich zu der Polycythaemia essentialis Milztuberkulose hinzugesellte. Andererseits fand Winter-  
nitz bei 26 aus der Literatur zusammengestellten an Milztuberkulose Leidenden in 6 Fällen Polyzythämie. Einzelne derartige



Fälle sind von Jedwabnik, Douglas und Eisenbrey, Lederer, Ren-  
nen und Leon-Kindberg und Garein veröffentlicht worden. Manche  
dieser Fälle sind in Wirklichkeit wahrscheinlich symptomatische  
Polyzythämien gewesen, bei denen eine gleichzeitige Lungen-  
tuberkulose die Respirationsfläche der Lunge dermassen verklei-  
nert hat, dass dadurch eine mangelhafte Oxydation des Blutes  
in den Lungen und hierdurch eine symptomatische Polyzythämie  
entstand. So sind die meisten Forscher jetzt der Ansicht, dass die  
Vergrösserung der Milz bei Polycythaemia essentialis lediglich  
eine kompensatorische Massnahme ist, denn die Milz funktioniert  
ja als Blutreservoir und nimmt zugleich auf irgendeine Weise  
an dem Zerfall der roten Blutkörperchen teil.

Da bei der Polycythaemia essentialis mehrere der Perniziosa  
entgegengesetzte Symptome auftreten und die Anaemia perniciosa  
durch Mangel an *intrinsic factor* im Magen hervorgerufen wird,  
ist man auch auf den Gedanken gekommen, dass eine Überpro-  
duktion des bei der Bildung der roten Blutkörperchen notwen-  
digen *intrinsic factor* vielleicht Polycythaemia essentialis auslösen  
könne. Für diese Auffassung tritt am nachdrücklichsten Hitzen-  
berger ein. Da wir aber die Zusammensetzung des *intrinsic factor*  
noch nicht kennen und daher seine Menge im Magensaft nicht zu  
bestimmen vermögen, ist es sehr schwer, Schlüsse auf den Anteil  
des *intrinsic factor* bei der Entstehung der Polycythaemia essen-  
tialis zu ziehen. Wie man angenommen hat, sprechen jedoch ge-  
wisse Umstände dafür, dass die Überproduktion von *intrinsic*  
*factor* der Hauptfaktor beim Zustandekommen der Polycythaemia  
essentialis ist. So findet man bei Ulens oft ziemlich hohe Erythro-  
zytenzahlen, und da sich an das Ulens im allgemeinen eine Hyper-  
sekretion anschliesst, hat man sich gedacht, dass vielleicht auch  
die Menge des *intrinsic factor* vermehrt sei und so jene Zunahme  
der Erythrozytenzahl verursachen könne.

Tuchfeld und Morris treten ausser Hitzenberger für die Theorie  
ein, dass die Polycythaemia essentialis durch eine Überproduk-  
tion von *intrinsic factor* hervorgerufen werde. Barath und Fülöp  
versuchten zu zeigen, dass bei der Polycythaemia essentialis wirk-  
lich mehr *intrinsic factor* als gewöhnlich abgesondert wird, indem  
sie täglich drei Polycythaemia essentialis-Patienten eine reichliche  
Fleischmahlzeit verzehren liessen, den aus dieser Speise entstan-  
denen Chymus aus dem Magen herausaugten und ihn dann Ana-

mia perniosa-Patienten per rectum gaben. Obgleich bei diesen eine deutliche Retikulozytose entstand, ist es natürlich sehr schwer, aus dem Versuch Schlüsse auf die Mengen des intrinsic factor zu ziehen. Für die Richtigkeit dieser Theorie spricht nach der Ansicht von Morris, Oerting und Briggs und Hitzenberger auch die Tatsache, dass in gewissen Fällen die Erythrozytenzahl bei den Polycythaemia essentialis-Patienten bedeutend sank, wenn bei ihnen fortgesetzt Magensaft ausgehebert wurde. Zieht man jedoch die bei Polycythaemia essentialis gewöhnlichen Spontanremissionen in Betracht, so könnte ein derartiger Versuch nur beweiskräftig sein, wenn ein grosses Material sowie ein von gesunden Personen erhaltenes Vergleichsmaterial vorläge.

Auf die Theorie gestützt, ist versucht worden, die Polycythaemia essentialis sowohl mit Röntgentherapie auf die Pylorusregion als mit einer möglichst totalen Resektion des Magens zu behandeln. Obwohl man in solchen Fällen bei der Polyzythämie mitunter eine deutliche Besserung erzielt, kann das Ergebnis meines Erachtens nicht als für eine Überproduktion von intrinsic factor beweisend gelten, denn es ist ja natürlich, dass diese Massnahmen, die sich auf Organe beziehen, welche nachweislich eine zentrale Rolle bei der Bildung der roten Blutkörperchen spielen, auch in dem Fall die Erythrozytenzahl herabsetzen würden, wenn die Funktion dieser Organe nicht gesteigert, sondern die gewöhnliche wäre. Gegen den ätiologischen Wert des intrinsic factor spricht direkt, dass auch eine sehr reichliche Lebermedikation keine Polyzythämie hervorruft.

Trotz dieser vielen Beobachtungen und Vermutungen müssen wir vorläufig annehmen, dass die Ätiologie der Polycythaemia essentialis heute ebenso unbekannt ist wie damals, als Vaquez diese Krankheit zum ersten Male beschrieb.

Was die Pathogenese der Krankheit anbelangt, könnte entweder eine ungewöhnlich grosse Neubildung von Blut, ein ungewöhnlich hohes Alter der roten Blutkörperchen oder eine Verhinderung des Zerfalls der Erythrozyten oder alle diese Faktoren zusammen in Frage kommen. Der erste Faktor, die ungewöhnlich starke Neubildung, ist bei der Krankheit sicher vorhanden, denn bei der Obduktion kann man ja in diesen Fällen regelmässig konstatieren, dass das Knochenmark fast durchgehend zu aktivem rotem Mark geworden ist, und dieser Faktor ist bestimmt der wichtigste patho-

genetische Faktor der Krankheit. Auf eine gesteigerte Neubildung von Blut weisen auch die oft im Blute vorkommenden Jugendformen der Blutkörperchen hin. Genaue Bestimmungen des Alters der Blutkörperchen bei Polycythaemia essentialis sind meines Wissens nicht ausgeführt worden. Der Zerfall des Blutes hinwieder dürfte bei der Krankheit jedenfalls nicht vermindert sein, da mit ihr oft ein erhöhter Ikterusindex oder positiver Meulengrachtscher Versuch einhergeht. Dies hat man darauf zurückführen wollen, dass von den Blutkörperchen selbstverständlich eine grössere Menge als gewöhnlich zerfällt, weil auch ihre Zahl grösser als gewöhnlich ist. Das ist denn auch natürlich, aber andererseits ist auch der Plasmagehalt bei Polycythaemia essentialis vermehrt. Minot und Buckman, Zadek und Paschkis und Diamant haben ausserdem auch direkt nachweisen können, dass der Zerfall des Blutes bei Polycythaemia essentialis nicht vermindert ist.

Da bei den osteuropäischen Juden ausser Polycythaemia essentialis auch zahlreiche Thromboangitis obliterans vorkommt, haben Reznikoff, Foot und Bethea angenommen, dass die von ihnen in einigen Polycythaemia essentialis-Fällen gefundene Verdickung der Wand der Kapillaren des Knochenmarkes Sauerstoffmangel im Knochenmark und dadurch Polyzythämie hervorrufen könne. Morawitz konnte jedoch zeigen, dass die Respiration der Gewebe bei Polycythaemia essentialis nicht gesteigert ist, und Röver und Koranyi, dass das Hämoglobin in diesen Fällen den Sauerstoff ebensogut wie bei Gesunden zu binden vermag, so dass der Sauerstoffmangel in den Geweben nicht die Ursache der Polycythaemia essentialis sein dürfte, wie er es bei der symptomatischen Polyzythämie ist.

### *Eigene Untersuchungen.*

Mein Material umfasst sämtliche Polyzythämiefälle, die während der Jahre 1928—1943 in der I. und II. medizinischen Klinik behandelt worden sind und in denen keine bekannte Ursache festzustellen war, die man für den Sauerstoffmangel und damit für die symptomatische Polyzythämie hätte verantwortlich machen können. Ich habe mein Material in zwei Teile geteilt, zu deren einem alle die Fälle gehören, die ich als sichere Fälle von Polycythaemia essentialis aufgefasst habe. In diesen übersteigt die Erythrozyten-

zahl die von Harrop und Wintrobe als obere Grenzen für die normalen Werte der roten Blutkörperchen angenommenen Werte 6.2 Millionen bei Männern und 5.4 Millionen bei Frauen, abgesehen von einem männlichen Patienten, dessen höchste Erythrozytenzahl 6.18 Millionen war. Ihn habe ich jedoch darum in diese Gruppe gestellt, weil die bei ihm anderwärts ausgeführten Bestimmungen der roten Blutkörperchen zu wiederholten Malen bedeutend höhere Erythrozytenzahlen ergeben hatten. Besonders für die Männer ist der Grenzwert von Harrop und Wintrobe recht hoch, und über ihn hinausgehende Werte können meiner Ansicht nach mit Sicherheit als polyzythämisch betrachtet werden. Auch bei den Frauen sind Erythrozytenwerte, die 5.4 Millionen überschreiten, recht selten, und auch sie dürfen wohl als polyzythämisch gelten. Nur bei einer Patientin meines Materials unterschreitet die Zahl der roten Blutkörperchen ausserdem den Grenzwert der Männer. Wenn die Erythrozytenzahl bei manchen Blutuntersuchungen immer 5.4 Millionen unterschreitet, dürfte es sich meiner Ansicht nach auch bei den Frauen nicht um Polycythaemia essentialis handeln können. Da andererseits der Grenzwert von Harrop und Wintrobe für die männlichen Patienten recht hoch ist, so dass sich als Differenz der Grenzwerte der Männer und Frauen 0.8 Millionen statt der gewöhnlichen 0.5 Millionen ergibt, so habe ich aus den männlichen Patienten, bei denen die Erythrozytenzahl zwischen 5.4 und 6.2 Millionen liegt und keine bekannte Ursache zu der Erhöhung der Erythrozytenzahl vorhanden ist, eine eigene Gruppe gebildet. In diese Gruppe meiner unsicheren Fälle gehören 11 männliche Patienten, während sich die sicheren zusammen auf 30 Fälle belaufen.

Wie ich im Zusammenhang mit den möglichen ätiologischen Faktoren der Krankheit erwähnte, ist die Polycythaemia essentialis bedeutend häufiger bei Männern als bei Frauen festgestellt worden. Die Verhältniszahlen variieren von 2:1 bis 3.5:1. Auf den Wert der so gefundenen Verhältniszahl wirkt natürlicherweise in hohem Grade die für die Männer und die Frauen gesondert vorgenommene Bestimmung der Grenzwerte ein.

Wenn die Grenzwerte, wie in den sicheren Fällen meines Materials, weit auseinandergehen, wird die erwähnte Verhältniszahl selbstverständlich bedeutend kleiner. So waren von den 30 sicheren Fällen meines Materials nur 16 Männer und nicht weniger als

14 Frauen. Als Verhältnis der Geschlechter ergibt sich demnach 1.1:1. Ziehen wir andererseits auch alle unsicheren Fälle in Betracht, wobei Männer insgesamt 27 und Frauen 14 zu zählen sind, so nähert sich das Verhältnis der von Lucas gefundenen Verhältniszahl 2:1 und beträgt 1.9:1. Diese Verhältniszahl ist jedoch offenbar zu gross, denn dabei ist ja für die Männer und die Frauen der gleiche Grenzwert genommen. Auf Grund meines Materials, dessen Fälle aus allen Teilen Finnlands in die Universitätskliniken geschickte Patienten sind, möchte ich also behaupten, dass die Polycythaemia essentialis auch in Finnland bei Männern etwas öfter als bei Frauen vorkommt, dass aber die Zahl der an dieser Krankheit leidenden Männer doch wahrscheinlich nicht die doppelte Anzahl der Frauen erreicht.

Polyzythämie war, wie bemerkt, ungewöhnlich häufig unter den Juden angetroffen worden. In Finnland werden Juden recht selten in den Universitätskliniken behandelt, da deren Patienten vom Lande stammen und die Juden vorwiegend in den Städten wohnen. Es dürfte daher erwähnenswert sein, dass einer von den unsicheren Fällen meines Materials ein Jude war.

Sichere hereditäre Fälle enthält mein Material nicht. Eine Patientin ist jedoch erst 20 Jahre alt, als die Krankheit bei ihr festgestellt wird, und ausserdem wird diese Feststellung zufällig gemacht, als die Patientin von einer Lungenentzündung befallen ist. Abgesehen von einer ungewöhnlich starken Röte, die sie gehabt hat, solange sie sich erinnern kann, hat sie keine Beschwerden gehabt. Das Bild der Krankheit entspricht bei ihr infolgedessen am ehesten dem der hereditären Polyzythämie. Es tritt bei ihr keine Leukozytose auf, und ihr Blut enthält keine Jugendformen von Blutkörperchen. Als ein sicherer hereditärer Fall kann die Patientin indessen nicht betrachtet werden, da über ihre Eltern und Schwestern keine Untersuchungen ausgeführt worden sind. Sie hat fünf Schwestern. Alle diese und auch die Eltern sind gesund und haben keine Symptome einer etwaigen Polyzythämie und auch keine besonders starke Röte wie die Patientin. Das Alter der Patientin, 20 Jahre, gehört zwar zu den niedrigsten Befunden bei der eigentlichen Polycythaemia essentialis, spricht aber nicht entscheidend gegen die Diagnose Polycythaemia essentialis, denn die Krankheit ist ja in ein paar Fällen auch bei Kindern festgestellt worden.

In der Anamnese von fünf sicheren Patienten finden sich Daten über das Vorkommen einer ungewöhnlich starken Röte in der Familie. Eine solche Röte hatten der Vater bzw. die Mutter je eines Patienten, der Vater und der Grossvater eines und der Onkel eines Patienten, und in der Familie eines trat sie überhaupt auf. In dem letzten dieser Fälle hatten alle sieben Kinder des Patienten eine ausserordentlich intensive Röte. Auf Grund derartiger Angaben kann man jedoch nicht annehmen, dass es sich in diesen Fällen um hereditäre Polyzythämie gehandelt hätte.

Als weitere mögliche ätiologische Faktoren erwähnte deutliche innersekretorische Störungen wiesen zwei sichere weibliche Patienten auf. Die eine hatte Struma und Thyreotoxikose, die im allgemeinen nicht bei Polyzythämie gefunden worden sind, und die andere einen Nebennierentumor. Zu den innersekretorischen Störungen sind meiner Ansicht nach auch die Menstruationsstörungen ohne deutliche gynäkologische Ursachen bei Frauen im geschlechtsreifen Alter zu rechnen.

In meinem Material finden sich 14 Patientinnen. Bei vier von diesen enthält der Krankheitsbericht keine klaren Angaben über die Menses. Bei 5 der übrigen 10 begann die Krankheit erst deutlich nach dem Klimakterium Symptome zu geben, bei einer im Alter von 45 Jahren, wo zugleich die Menstruationen ausblieben. In dem letzterwähnten Fall ist es sehr wohl möglich, dass die Menses der Patientin wegen des frühen Klimakteriums aufhörten, obgleich es andererseits ebensogut denkbar ist, dass der Beginn der Polyzythämie einen Anteil an dem Ausbleiben der Menstruationen gehabt hat. Übrig sind 4 Patientinnen. Von diesen kam eine mit 53 Jahren in Behandlung. Ihre Menses hatten aufgehört, als sie 51 Jahre alt war. Als Symptom der Polyzythämie trat bei ihr hauptsächlich Kopfschmerz auf, an dem sie mehrere Jahre litt. Infolge der unbestimmten Formulierung lässt sich nicht ausmachen, ob sie schon vor dem Ausbleiben der Menstruationen von Polyzythämie herrührenden Kopfschmerz gehabt hatte. Von den 3 übrigen Patientinnen, deren Alter beim Auftreten der ersten Krankheitszeichen 20, 25 und 37 Jahre betrug, hörten die Menses bei zwei zu Beginn der Krankheit ganz auf und wurden bei einer unregelmässig und deutlich spärlicher als früher. In meinem Material blieben die Menstruationen also bei allen Patientinnen, die noch nicht das Klimakterium erreicht hatten und über deren Menses Angaben vorliegen, schon gleichzeitig mit dem Erscheinen der ersten anderen Symptome entweder ganz aus oder wurden wenigstens spärlicher als früher.

In Abbildung 1 gebe ich das Alter der Patienten meines Materials zu der Zeit, als die Krankheit bei ihnen die ersten subjektiven Symptome auslöste. Die unsicheren Fälle sind in der Abbildung durch Schraffen bezeichnet. Das Alter der sicheren Fälle war bei dem Auftreten der ersten Symptome der Krankheit meistens 31—

50 Jahre. In vier sicheren Fällen liegt über den Anfang der Krankheit keine sichere Angabe vor, und zwei von ihnen waren, als sie in Behandlung kamen, symptomlos. Von den unsicheren Fällen hinwieder zeigten 5 keine Symptome, in einem Fall ist über den Anfang der Krankheit nichts mitgeteilt, und bei den anderen begann die Krankheit im Alter von 31—50 Jahren. Wie ich schon oben erwähnte, war der jüngste Fall meines Materials eine 20jährige Frau, deren Krankheitsbild ziemlich lebhaft an die Form der hereditären Polyzythämie erinnerte, ohne dass man mit Bestimm-

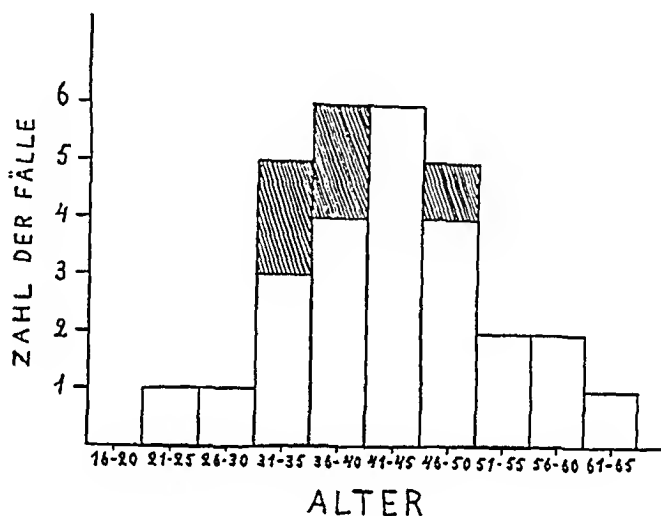


Abb. 1.

heit behaupten kann, dass es sich um die hereditäre Krankheitsform handle.

Die meisten sicheren Fälle meines Materials kamen zum ersten Male mit 36—60 Jahren, also vorzugsweise in mittleren Jahren, in Behandlung. Von alten, über 60jährigen sicheren Fällen kam nur einer in Behandlung. Die Zahl der unsicheren Fälle ist so gering, dass bei ihnen der Zufall eine sehr grosse Rolle spielen kann. Sie kamen zum ersten Male in sehr verschiedenem Alter in Behandlung, die meisten jedoch in jüngeren Jahren als die sicheren Fälle, nämlich mit 26—40 Jahren.

Die Dauer der Symptome war bei den verschiedenen Patienten vor Beginn der Behandlung recht verschieden. Ein sicherer Fall erhielt sofort nach dem Erscheinen der ersten Symptome Therapie, bei den anderen sicheren Fällen war diese Zeit in 2 Fällen kürzer als  $\frac{1}{2}$  Jahr, in 4  $\frac{1}{2}$ —1

Jahr, in 2 1—2 Jahre, in 4 2—3 Jahre, in 3 3—4 Jahre, in 2 4—5 Jahre, in 1 5—6 Jahre, in 2 8—9 Jahre, in 1 9—10 Jahre und in 2 über 10 Jahre. In einem Fall sind als Dauer der Symptome unbestimmt mehrere Jahre angegeben, und in 3 Fällen findet sich über die Dauer keine Eintragung. 2 sichere Fälle kamen ohne durch Polyzzythämie hervorgerufene Symptome in Behandlung. Der eine von ihnen ist die schon früher erwähnte 20jährige Frau, die wegen Lungenentzündung in ein Provinzialkrankenhaus aufgenommen war, wo bei ihr eine deutliche Polycythaemia essentialis festgestellt wurde. Sie wurde auch später mehrere Male wegen Polyzzythämie in der I. medizinischen Klinik behandelt. Die Symptomlosigkeit ihrer Krankheit und ihr junges Alter erregen den Verdacht, dass die hereditäre Form der Polyzzythämie vorgelegen haben könnte. Der andere symptomlose, aber sichere Fall ist desgleichen eine Frau, und diese kam im Alter von 57 Jahren wegen Struma, Thyreotoxikose und Herzfehler in Behandlung. Sie hatte eine offenbar von der Thyreotoxikose herrührende Arrhythmia absoluta ohne deutliche Symptome von Herzinsuffizienz, und ihre Polyzzythämie verschwand nicht während der Behandlung, wie die durch Herzinsuffizienz hervorgerufene Polycythaemia symptomatica im allgemeinen verschwindet. Da die Erythrozytenzahl bei ihr ausserdem einmal über 7 Millionen und auch bei allen anderen Bestimmungen nur etwas unter 7 Millionen betrug und mithin bedeutend höher anstieg als in den im ersten Teil meiner Arbeit veröffentlichten durch Herzfehler ausgelösten Fälle von Polycythaemia symptomatica, so habe ich diesen Fall als eine sichere Polycythaemia essentialis betrachtet.

Nur sechs meiner unsicheren Fälle hatten Symptome, die auf Polyzzythämie zurückgeführt werden können. Als solche Symptome habe ich aufgefasst: Kopfschmerz in 2 Fällen, einen Blutpfropf im Bein einmal, einen Blutpfropf im Herzen einmal und einen masslichen Gehirnthrombus einmal, wobei der Patient zweimal nacheinander ohnmächtig wurde und danach ungefähr eine Stunde bewusstlos war. In 5 unsicheren Fällen ist der Patient wegen anderer Beschwerden ins Krankenhaus gekommen und die Polyzzythämie nur ein Nebebefund gewesen. Die eigentliche Krankheit bestand in diesen Fällen je einmal in Magenkrebs nebst Lungenmetastasen, in Nierenstein, Herzinsuffizienz, dyspeptischen Beschwerden sowie in Hypertonie und Bandwürmern.

Der Fall, in dem Magenkrebs nebst Lungenmetastasen vorlag, könnte auch eine von den Lungenmetastasen herrührende symptomatische Polyzzythämie sein. Da jedoch die Lungenveränderungen des Patienten verhältnismässig unbedeutend waren und im Schrifttum keine Angaben über durch Lungenmetastasen verursachte symptomatische Polyzzythämie zu finden sind, habe ich es als richtiger betrachtet, den Fall zu den essentiellen Polyzzythämien zu rechnen. Dieser Patient hatte weder Aszites noch eine



andere Flüssigkeitsansammlung in einer Körperhöhle, so dass die Erhöhung der Erythrozytenzahl nicht auf einer durch Flüssigkeitsverlust hervorgerufenen Pseudopolyzythämie beruht haben kann. Den Fall mit Herzinsuffizienz habe ich zu den unsicheren essentiellen Polyzythämien gestellt, weil die Polyzythämie bei ihm nicht verschwand, obgleich die Herzinsuffizienz des Patienten geheilt wurde. Der Patient hatte keinen Klappenfehler, bei dem möglicherweise Polyzythämie auch ohne Herzinsuffizienz vorgelegen hätte, sondern Myodegeneratio cordis. Der Fall, der sowohl erhöhten Blutdruck als Bandwurm hatte, zeigte als subjektives Symptom auch den bei Polyzythämie auftretenden Schwindel, da er aber andererseits die allerkleinsten Erythrozytenwerte, 5.5 Millionen bei einem Mann, hatte und da ebensogut auch der Bandwurm das einzige Symptom des Patienten ausgelöst haben kann, habe ich dasselbe nicht mit Sicherheit auf Polyzythämie zurückgeführt. Auch die Hypertonie konnte in diesem Fall Schwindel verursachen. Ein unsicherer Fall hatte als andere Krankheit einen leichten Diabetes renalis. Seine Harnmengen waren ganz normal, weshalb es sich wohl nicht um eine durch Polyurie hervorgerufene Pseudopolyzythämie gehandelt haben kann.

Als erstes subjektives Symptom der sicheren Fälle von Polycythaemia essentialis zeigte sich das gewöhnlichste Symptom der Polyzythämie, Kopfschmerz, und gleichzeitiger Schwindel in 7 Fällen, ausschliesslich Kopfschmerz in 3 Fällen und bloss Schwindel in 5 Fällen. In einem Fall bestand das erste Symptom bei dem Patienten in oft wiederkehrenden Sehstörungen, deren Ursache nicht ermittelt werden konnte. Da sie ohne therapeutische Massnahmen in einigen Minuten vorbeigingen, dürfte es sich nicht um Thrombenbildungen oder Blutungen in den Augenadern, sondern um eine Art spastischen Zustands gehandelt haben. Vertaubungsgefühl in den Händen und Füßen war in einem Fall das erste Symptom, in 3 Fällen eine Blutung einmal aus der Zunge und einmal aus der Nase sowie in dem dritten Fall eine Blutung aus dem Darmkanal. In einem Fall verspürte der Patient zuerst Müdigkeit, und in 2 Fällen bestand das erste Symptom darin, dass die Haut eine stärker rote Färbung als gewöhnlich annahm. In 3 Fällen liegt keine Mitteilung über das erste subjektive Symptom vor, und 2 Fälle waren in bezug auf Polyzythämie symptomlos. Der eine von diesen hatte zwar während seines ganzen Lebens eine intensive rote Hautfarbe gehabt, hat aber nicht darüber geklagt. 2 der Fälle begannen mit Symptomen einer atypischen Leukämie, und in diesen beiden Fällen klagten die Patientinnen über Ermüdung als erstes Symptom, die eine dazu über ein Völlegefühl in der linken Seite.

Die gewöhnlichsten Symptome der Polycythaemia essentialis, Kopfschmerz und Schwindel, traten, nachdem sich die Krankheit zu voller Intensität entwickelt hatte, in meinem Material folgendermassen auf: Kopfschmerz in 21 sicheren und 3 unsicheren und Schwindel in 14 sicheren und 2 unsicheren Fällen. Der bei Polycythaemia essentialis vorkommende Kopfschmerz ist meistens ein solcher des Cephalalgia intermittens-Typus, aber aus meinem Material lassen sich diesbezüglich keine sicheren Schlüsse ziehen.

Schleimhautblutungen wurden in 13 sicheren Fällen angetroffen. Nasenbluten hatten 8 Patienten, dazu hatten solches 2 oft in der Kindheit gehabt, wogegen es während der Krankheit nicht mehr beobachtet wurde. Zahnfleischblutungen fanden sich bei 5 Patienten, bei einem ausserdem Blutung aus dem Zungenrücken, bei einem aus den Lippen und bei einem aus dem Darmkanal. Die Ursache dieser Blutungen dürfte in einer ungewöhnlich starken Füllung der Schleimhautblutgefässe zu suchen sein.

Grosse Viskosität des Blutes verursacht zusammen mit einer verhältnismässig langsamen Strömung des Blutes in den Kapillaren und mit manchmal vorkommender Erhöhung der Thrombozytenzahl andererseits oft Thrombosen in verschiedenen Teilen des Körpers. 4 sichere Fälle hatten deutliche durch die Krankheit hervorgerufene Thrombosen: bei einem wurden in der Schleimhaut der Harnblase hämorrhagische Flecken festgestellt, und derselbe Patient hatte im rechten Fusse Schmerzen, die von früheren Thromben im Bein hergerührt haben können, bei einem bestand lange ein Verlaubungsgefühl in der linken Hand und dem linken Bein, und zuletzt entwickelte sich bei ihm eine linksseitige Lähmung, einer hatte einen Lungenembolus, und bei demselben Patienten zeigte sich auch ein Blutpfropf im linken Unterschenkel, und schliesslich hatte ein Patient zahlreiche Thromben in verschiedenen Teilen des Körpers, davon die bedeutendsten im Gehirn und in den Nieren. Für diese Thrombosen war es in allen Fällen charakteristisch, dass sich das Krankheitsbild allmählich entwickelte, wobei der Thrombus zuerst gewöhnlich mehrere Tage leichte und unbestimmte Symptome gab, bis diese nach und nach ihre volle Stärke erreichten.

Von den unsicheren Fällen hatte einer anamnestisch einen deutlichen Thrombus in der rechten Fusswurzel und einer eine deutliche Gehirnthrombose gehabt, während ein anderer Sym-

ptome zeigte, die auch in hohem Grade als Gehirnthrombose imponierten. Er wurde nämlich zweimal nacheinander ohnmächtig und war darauf ungefähr eine Stunde bewusstlos. Einer hatte ausserdem in verhältnismässig niedrigem Alter, mit 39 Jahren, einen Herzinfarkt. Oppenheimer hat einen Herzinfarkt im Zusammenhang mit Polycythaemia essentialis schon bei einem 28jährigen Patienten festgestellt.

Der Körperbau war bei den Patienten meines Materials meist entweder gewöhnlich oder kräftig, das Gewicht bei fast allen normal. Dies geht aus den folgenden Zahlen hervor. Von den sicheren Fällen waren schwächlich 1, ziemlich schwächlich 2, von gewöhnlichem Bau 9, ziemlich stark 4 und kräftig 8. In 6 Fällen ist die Konstitution nicht definiert. Der Körperbau der unsicheren Fälle war zweimal gewöhnlich, viermal ziemlich stark und viermal kräftig. Über einen fehlen Angaben. Das Körpergewicht war bei den sicheren Fällen in 11 gewöhnlich, in 2 bestand ein deutliches Untergewicht und in 5 ein Übergewicht. Die Körperlänge von anderen ist nicht bekannt, warum der zu besprechende Vergleich bei ihnen nicht ausgeführt werden konnte. Von den unsicheren Fällen hatten 3 ein gewöhnliches Körpergewicht, einer zu geringes und 2 zu hohes Gewicht.

Schon Vaquez bemerkte, dass die Farbe der Haut bei Polycythaemia essentialis stärker als gewöhnlich rot ist und dass sie von der Farbe der zyanotischen Haut abweicht, obgleich die Haut auch in solchen Fällen ausser der Röte eine blaue Komponente enthalten kann. Die Hautfarbe ist jedoch stets deutlich vorwiegend rot, und die blaue Farbe tritt zurück. Diese Veränderung der Hautfarbe findet sich ausschliesslich an den dem Licht ausgesetzt gewesenen Körperteilen, und sie ist am intensivsten im Gesicht, besonders an der Nase und den Ohren, also an den vorstehenden Körperteilen. Ausserdem bemerkt man sie oft an den Füßen. Im Gesicht treten oft Teleangiektasiebildungen auf. Seltener beobachtet man Rotfärbung der Haut auch am Halse, am oberen Teil des Thorax und in den Ellenbeugen. Wie R. Ehrström gezeigt hat, beruht diese Veränderung der Hautfarbe wenigstens teilweise auf pathologischen Veränderungen in der Haut, und zwar auf einer krankhaften Erweiterung der Hautblutgefässe.

Die Farbe der Haut ist in 26 sicheren Fällen beachtet worden. Sie war im allgemeinen rot oder die rote war zumindest stärker als die anderen festgestellten Färbungen. Die Haut war als rot beschrieben in 11 Fällen, als dunkelrot in 4, als kupferrot in 1, als braunrot in 1, als stark himbeerrot in 1 Fall, b'aurot war sie in 3

Fällen, dunkel blaurot in 2, violettrot in 2 und gewöhnlich in 1. In dem letztgenannten Fall waren jedoch die Finger deutlich stärker rot als gewöhnlich. Die rote oder vorwiegend rote Farbe trat mit der erwähnten Ausnahme in allen Fällen im Gesicht, in 10 Fällen auch an den Händen, in 3 auch an den Beinen und in 7 ausserdem am Halse auf. Als zyanotisch war die Hautfarbe keinmal beschrieben. In den unsicheren Fällen war die Farbe des Gesichtes 7 mal rot, 2 mal gewöhnlich und 2 mal zyanotisch.

Die meisten Forscher haben gefunden, dass Herzerweiterung bei Polyeythaemia essentialis relativ selten ist, und zwar auch in den Fällen, in denen gleichzeitig Hypertonie vorliegt. So war in 58 % der von Lucas gesammelten 123 Fälle keine Herzhypertrophie vorhanden. In den 32 Fällen Futchers fand sich Herzhypertrophie nur zu 15 %. Zu ähnlichen Ergebnissen sind Brown und Giffin, Hollaender und Zadek gekommen. Zadek hat auch konstatiert, dass Arteriosklerose und Hypertonie bei Polycythaemia essentialis nur in demselben Masse wie im allgemeinen sonst bei gleichaltrigen Personen vorkommen, und ist mithin zu dem Resultat gelangt, dass die Polycythaemia essentialis nicht Herzhypertrophie, Hypertonie oder Arteriosklerose hervorruft. Del Baere erklärt, das Fehlen der Herzhypertrophie beruhe trotz der grossen Zunahme der Viskosität des Blutes darauf, dass für die Deckung des Sauerstoffbedarfs der Gewebe infolge der hohen Erythrozytenzahl eine kleinere Blutmenge als gewöhnlich erforderlich sei, so dass die Arbeit des Herzens bedeutend erleichtert werde. Weber ist daher der Ansicht, dass die Polyzythämie für Personen, die an Hypertonie leiden, recht vorteilhaft sei. Hess hat versucht, experimentell bei Tieren durch Vermehrung der Blutmenge Herzhypertrophie hervorzurufen, doch ist ihm dies nicht gelungen. Gewisse Forscher wollen so weit gehen, alle die Fälle dem Kreise der Polyeythaemia symptomtica zuzuzählen, in denen ein Herzfehler auftritt. Die Pulsfrequenz ist im allgemeinen normal, obwohl in einigen Fällen eine leichte Tachykardie wie auch bisweilen Herzklopfen beobachtet worden ist.

Gaisböck beschrieb 1905 eine Anzahl Polyeythaemia essentialis-Patienten, die nicht die gewöhnlich zu dem Krankheitsbild gehörende Vergrösserung der Milz, dagegen aber eine deutliche Hypertonie hatten. Derartige Fälle wurden später, von der Vaquezschen Krankheit getrennt, als Polyeythaemia essentialis des Gaisböcksehen Typus

bezeichnet. Heute ist diese Teilung der *Polycythaemia essentialis* in zwei Typen recht allgemein aufgegeben, und die Forscher sind der Ansicht, dass es sich in allen diesen Fällen um ein und dieselbe von Vaquez beschriebene Krankheit handelt, bei der die Vergrösserung der Milz keine *conditio sine qua non* ist, da auch Fälle von *Polycythaemia essentialis* ohne vergrösserte Milz, aber auch ohne Hypertonie, und andererseits Fälle sowohl mit vergrösserter Milz als auch mit Hypertonie festgestellt worden sind. Hypertonie hinwieder ist in dem Alter, in dem die Krankheit am häufigsten vorkommt, ein so gewöhnliches Symptom, dass sie nicht zur Aufstellung einer besonderen Krankheitsgruppe berechtigt, sondern das Auftreten der Hypertonie in manchen Fällen wird heutzutage allgemein als ein ganz von der Polyzythämie getrenntes, aber zufällig gleichzeitiges Symptom betrachtet.

In 12 der 30 sicheren Fälle meines Materials fand sich deutlich eine Hypertrophie und Linksdilatation des Herzens. In den unsicheren Fällen kam dies bei 3 Patienten vor. Eine deutliche Arteriosklerose wurde in 12 sicheren und 2 unsicheren Fällen konstatiert. In 5 sicheren Fällen ergab sich ausserdem röntgenologisch Aortensklerose.

Der Blutdruck war nur selten hoch angestiegen, und auch leichte Erhöhungen waren bei ihm relativ selten. In 23 sicheren Fällen schwankte der Blutdruck bei den verschiedenen Bestimmungen nur wenig und betrug in 4 Fällen 100—120 mm Hg, in 8 120—140, in 7 140—160, in 3 160—180 und in 1 200—220. Bei 6 Patienten waren die Variationen des Blutdruckes bei den verschiedenen Bestimmungen recht gross. So war der Blutdruck in 1 Fall 100—180, in 1 100—160, in 2 Fällen 120—160, in 1 180—220 und in 1 200—240 mm Hg. Bei 12 sicheren Patienten war er mithin bei allen Messungen normal, und bei 17 trat wenigstens bei einigen Messungen eine Hypertonie auf, die jedoch in 10 Fällen nicht 160 mm Hg überstieg. In sämtlichen Fällen ist die erste Bestimmung nach der Aufnahme des Patienten ins Krankenhaus unberücksichtigt gelassen worden, sofern sie bedeutend von den anderen Messungsergebnissen abwich. Über den Blutdruck eines sicheren Patienten finden sich keine Aufzeichnungen. Bei den unsicheren Fällen betrug der Blutdruck in 1 Fall 100—120, in 6 Fällen 120—140, in 2 140—160, in 1 160—200 und in 1 200—200 mm Hg. Hypertonie kam mithin in 4 von insgesamt 11 unsicheren Fällen vor, und nur in 2 von diesen war sie erheblich.

Die Pulsfrequenz war im allgemeinen normal und betrug in den sicheren Fällen bei 9 Patienten 65—75/Min., bei 13 75—85 und bei 4 85—95/Min. In einem Fall lag sie zwischen 135 und 145/Min., aber dieser Patient war nur ein paar Tage ante exitum in Behandlung. Für 3 Fälle fehlt eine Angabe über die Pulsfrequenz. So trat Bradykardie keinmal auf, und auch deutliche Tachykardie war selten. In den unsicheren Fällen war der Puls bei 2 Patienten 55—65, bei 4 65—75, bei 3 75—85 und bei 1 105—115/Min. In einem Fall wird eine Mitteilung über die Pulsfrequenz vermisst.

Trommelschlegelfinger sind nur von Lommel und Gaisböck in einigen Fällen von Polycythaemia essentialis festgestellt worden. In den Fällen meines Materials sind sie bei keinem Patienten vorgekommen.

Schstörungen sind nach Harrop und Wintrobe bei Polycythaemia essentialis häufig. In meinem Material finden sie sich nur in einem schon erwähnten Fall, in dem sie die ersten Symptome der Krankheit darstellten. In allen Fällen, wo die Augenhintergründe untersucht wurden, waren deren Blutgefässe auf typische Weise dilatiert.

Nach Harrop und Wintrobe sind auch dyspeptische Beschwerden im Zusammenhang mit Polycythaemia essentialis recht gewöhnlich. Auch Ulkus schliesst sich oft an Polycythaemia essentialis an. So konstatierten Willbur und Ochsner unter ihren 143 Polycythaemia essentialis-Fällen 12 Ulkuspatienten, also in etwa 8 % der Fälle.

Sowohl Ulkus als dyspeptische Beschwerden waren in meinem Material seltener. Unter den sicheren Fällen befanden sich nur 3 Dyspeptiker und ausserdem ein Ulkuskranke, woraus sich eine Ulkushäufigkeit von ca. 3% ergeben würde. Unter den unsicheren Fällen wiederum waren 1 Fall von Magenkrebs, 1 Dyspeptiker und 1 Ulkuskranke zu bemerken. Boyd erklärt die ungewöhnlich hohe Häufigkeit des Ulkus in Verbindung mit Polycythaemia essentialis daraus, dass dabei, entsprechend der allgemeinen Disposition zu Thrombose, auch in der Magenschleimhaut kleine Thromben entstehen, auf deren Grundlage sich dann Ulkus entwickelt.

Brown und Giffin haben eine Vergrösserung der Leber in 57 % ihrer Fälle angetroffen. In meinem Material war die Leber nur in 4 sicheren und 3 unsicheren Fällen vergrössert, und auch in diesen beruhte das wenigstens einmal auf der Herzinsuffizienz, an der der Patient gleichzeitig litt. Leberzirrhose ist bei Polycythaemia essentialis von Türk, Blad, Lommel, Rist, Mosse und mehreren anderen nachgewiesen worden. Mosse hat vorgeschlagen, die Fälle, in

denen Urobilin im Harn und Leberzirrhose vorkommt, als besonderen Typus abzutrennen. Nach der Ansicht der meisten Forscher ist die dann und wann konstatierte Leberzirrhose jedoch nur als eine Komplikation der Vaquezschen Krankheit zu betrachten. Bei einem Patienten meines Materials, bei dem eine Magenresektion ausgeführt wurde, zeigte sich bei Gelegenheit der Operation eine beginnende Leberzirrhose.

Die Milz ist bei Polycythaemia essentialis sehr oft vergrössert, aber ihre Schwellung ist doch keine *conditio sine qua non*. Nach Naegeli begegnet man einer Vergrösserung der Milz in 75 % der Fälle.

In meinen eigenen Fällen war die Milz deutlich palpatorisch in 11, ausschliesslich perkussorisch in 8 vergrössert, und in 11 Fällen konnte eine Milzschwellung auf keine Weise festgestellt werden. In den unsicheren Fällen war die Milz in 1 Fall palpatorisch und ebenso in 1 perkussorisch vergrössert.

Zu der Krankheit gesellen sich auch verhältnismässig oft Symptome von den Nieren in Form von Albuminurie, pathologischem Sediment und erhöhtem Reststickstoff. In meinem Material fand sich in 9 sicheren Fällen Albuminurie, ausserdem hatten 1 sicherer und 1 unsicherer Fall eine offenbar durch Nierenstase bedingte Albuminurie. Dazu wurde in 1 sicheren Fall eine starke Hämaturie mit anschliessender Albuminurie bei Niereninfarkt als Symptom konstatiert. Auch 2 unsichere Fälle hatten Albuminurie. Die Albuminmenge war, von dem Infarktfall abgesehen, in allen Fällen gering, sie betrug 0—2 ‰. Pathologisches Sediment hatten nur 4 und auch da nur Leukozyten. Der Reststickstoff wurde nur bei 8 Patienten bestimmt, und er war in 4 Fällen deutlich erhöht, in 4 dagegen normal. Der höchste Wert, 120 mg %, wurde bei der jungen Frau gefunden, bei der die Krankheit an die hereditäre Form erinnerte. Sie hatte jedoch keine Albuminurie. In den übrigen Fällen lag der Wert des Reststickstoffs, wenn erhöht, zwischen 55 und 63 mg %.

Die Erythrozytenzahl bewegt sich bei Polycythaemia essentialis oft zwischen 8 und 12 Millionen, doch sind auch Werte von 6—8 Millionen gewöhnlich. Der grösste sicher nachgewiesene Wert, 15 Millionen, ist von Seufert mitgeteilt worden. Der Durchmesser der roten Blutkörperchen ist im allgemeinen normal. Das Hämoglobin ist auch stark vermehrt, aber besonders in den späteren

Tabelle 1.

	Alter	Ge- schlecht	Hb Sahli	Erythrozyten Mill.	Färbeindex
1	55	♂	115—120	8.46—10.56	0.55—0.75
2	54	♂	100—140	4.96— 9.45	0.75—1.06
3	52	♂	128—139	8.04— 9.39	0.71—0.82
4	48	♀	110—115	7.63— 9.19	0.60—0.72
5	43	♂	118—142	7.08— 9.00	0.75—0.92
6	48	♂	111—126	6.70— 8.84	0.71—0.90
7	44	♂	112—133	6.61— 8.82	0.70—0.89
8	49	♂	120—130	7.65— 8.82	0.70—0.79
9	39	♂	110—130	6.40— 8.80	0.69—0.89
10	59	♀	52—117	3.03— 8.64	0.56—0.94
11	53	♀	115—125	7.02— 8.56	0.73—0.82
12	22	♀	137—155	7.02— 8.50	0.90—1.02
13	64	♂	130—130	7.59— 7.64	0.86—0.87
14	56	♀	107—117	4.93— 7.41	0.79—1.12
15	53	♀	50— 95	3.55— 7.25	0.59—0.84
16	55	♂	90—102	5.08— 7.25	0.71—0.90
17	48	♀	101—110	7.11— 7.22	0.70—0.76
18	32	♂	105	7.10	0.74
19	34	♂	102	7.10	0.72
20	38	♀	60—118	3.89— 7.06	0.77—0.84
21	57	♀	120—125	6.52— 7.03	0.85—0.92
22	41	♂	92—107	5.48— 7.02	0.66—0.92
23	60	♀	110—120	6.45— 6.86	0.85—0.92
24	43	♀	90— 97	6.00— 6.85	0.71—0.75
25	41	♂	120	6.72	0.90
26	57	♀	92—112	5.00— 6.50	0.86—0.92
27	38	♀	110—110	6.16— 6.48	0.85—0.90
28	38	♂	93—101	4.95— 6.30	0.78—0.98
29	49	♂	91—104	5.25— 6.18	0.81—0.89
30	26	♀	90—105	4.82— 5.45	0.90—0.97
31	50	♂	95— 95	6.14— 6.16	0.77—0.77
32	35	♂	96—102	5.32— 6.05	0.84—0.90
33	39	♂	103—123	5.28— 5.98	0.96—1.06
34	27	♂	108—110	5.68— 5.94	0.93—0.96
35	56	♂	115—118	5.80— 5.90	0.99—1.00
36	39	♂	100—108	5.21— 5.84	0.93—0.96
37	46	♂	90—100	5.12— 5.73	0.87—0.92
38	30	♂	85—101	4.85— 5.63	0.88—0.90
39	33	♂	102—105	5.30— 5.60	6.91—0.98
40	38	♂	94—102	5.08— 5.60	0.91—0.92
41	68	♂	105	5.52	0.95



Stadien der Krankheit doch nicht so sehr wie die Zahl der Erythrozyten, so dass der Färbeindex dann kleiner als gewöhnlich wird. Verhältnismässig oft findet man Polychromasie und basophile Punktierung sowie einige Normoblasten im Blute.

In Tabelle 1 gebe ich die Beobachtungen über das rote Blutbild meines Materials wieder. Die Fälle sind nach den sinkenden Erythrozytenzahlen geordnet, und von jedem Fall ist sowohl die

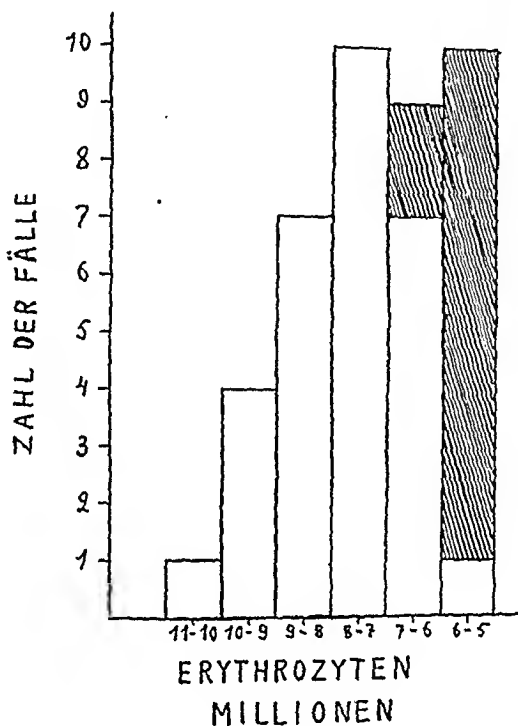


Abb. 2.

niedrigste als die höchste Erythrozytenzahl angeführt. Wie aus der Tabelle hervorgeht, ist der grösste Wert von den höchsten Werten der Fälle 10.56 und der kleinste 5.45 Millionen. Die Verteilung der höchsten Zahlen der roten Blutkörperchen wird andererseits aus Abbildung 2 ersichtlich.

Die höchsten Werte des nach Sahli bestimmten Hämoglobins variieren bei den sicheren Fällen von 140—95. Bei den unsicheren Fällen sind diese Zahlen 6.16—5.52 Millionen und 123—95 (Sahli). Unter den niedrigen Werten treten deutlich anämische Werte bei 2 Patientinnen, den Fällen 10 und 15, auf, bei denen die Krank-

heit in ihrem Endstadium leukämisch wurde, ebenso in Fall 20 infolge einer Blutung im Zusammenhang mit der Magenresektion.

Das Hämoglobin ist bisweilen weniger erhöht als die Erythrozytenzahl, so dass der Färbeindex in 6 sicheren Fällen wenigstens bei einigen Bestimmungen deutlich herabgesetzt ist. In 11 sicheren Fällen hinwieder ist der Färbeindex bei einigen Bestimmungen erhöht. In den unsicheren Fällen tritt dagegen kein niedriger Färbeindex auf. Ein erhöhter Färbeindex wurde in 6 unsicheren Fällen bei allen und ausserdem in 2 bei einigen Bestimmungen gefunden. Als Normalwerte des Färbeindex habe ich die Werte 0.71—0.90 betrachtet, weil das Hämoglobin nach Sahli bestimmt worden ist.

Der Durchmesser der roten Blutkörperchen ist nur bei 3 sicheren und 2 unsicheren Fällen festgestellt worden, und er war bei den sicheren Fällen 7.86, 7.83 und 7.30 und bei den unsicheren 7.20 und 6.84  $\mu$ . Normoblasten hatten nur 2 sichere Fälle im Blute. Bei dem einen betrug ihre Menge 1—3: 200 und bei dem anderen 1: 500—7: 200. Beide Fälle verwandelten sich allmählich in eine typische myeloische Leukämie.

Die roten Blutkörperchen sind bei Polycythaemia essentialis in der Regel von gleicher Form und Grösse, obwohl manchmal eine leichte Anisozytose und Poikilozytose zu beobachten ist. Dies findet sich in meinem Material in 6 sicheren Fällen.

Leukozytose gehört fast regelmässig zu dem Krankheitsbild, obgleich dann und wann auch gewöhnliche Leukozytenzahlen vorkommen. Die an die Krankheit anschliessende Leukozytose wurde zuerst von Türk festgestellt, wiewohl auch bei dem Vaquezschen Fall eine deutliche Leukozytose, 30,000 weisse Blutkörperchen, vorlag, ein Symptom, das Vaquez jedoch übersehen zu haben scheint. In dem von Lucas gesammelten Material waren die Leukozyten in 96 Fällen berechnet worden, und bei 65 von diesen, d. h. in 67.7 %, überstieg die Leukozytenzahl 10,000. Im allgemeinen beträgt die Zahl der Leukozyten nach Harrop und Wintrobe bei Polycythaemia essentialis 10,000—25,000. Die höchste Leukozytenzahl, 91,000, hat Cautley angegeben.

Bei der Differenzierung der weissen Blutkörperchen findet man im allgemeinen, dass die Leukozytose fast gänzlich von der Vermehrung der myeloischen Zellen herrührt. So ist die Zahl der Lymphozyten relativ vermindert, aber absolut betrachtet meistens.

normal. Myelozyten kommen in manchen Fällen zu 1—2 % im Blute vor und bisweilen selten auch einige Myeloblasten. Die Zahl der Eosinophilen und Basophilen ist auch ab und zu erhöht. Leukopenie ist dagegen kaum je in unbehandelten Fällen, wohl aber nach Röntgen- oder Arseniktherapie zu bemerken.

In Tabelle 2 gebe ich für mein Material die Zahl der Leukozyten, das Lymphozytenprozent und die absolute Zahl der Lymphozyten an. Von allen sind sowohl der grösste als der kleinste Befund angeführt. Die Zahl der weissen Blutkörperchen stieg in 20 Fällen oder 66.7 % auf mindestens 10,000; der niedrigste Wert war 10,000, der höchste 49,900. In 8 der übrigen 10 Fälle überschritt die Zahl der weissen Blutkörperchen ausserdem den Wert 8,000, der oft als die obere Grenze der normalen Leukozytenzahl betrachtet wird, und nur in 2 Fällen war die Menge der weissen Blutkörperchen die gewöhnliche, 6,100 und 7,800. In den unsicheren Fällen überstieg die Leukozytenzahl 10,000 nur bei 2 Patienten, war bei 1 grösser als 8,000, aber kleiner als 10,000 und in 7 Fällen ganz normal. In 1 unsicheren Fall lag eine leichte Leukopenie, 5,200, vor.

Das Lymphozytenprozent schwankt sehr stark, indem der kleinste Wert 1.0 % und der grösste 42 % ist. Mustert man die absoluten Werte der Lymphozyten durch, so sieht man, dass diese Zahlen einander etwas näher liegen, obwohl auch bei ihnen Schwankungen vorkommen. Der niedrigste Wert ist 286 und der höchste 7,235. Betrachten wir als normale prozentuale Mengen der Lymphozyten die Werte von Bloom, 20—25 %, und als normale Mengen der Leukozyten die Werte 6,000—8,000, so erhalten wir als normale Mengen der Lymphozyten 1,200—2,000. Nur in 6 sicheren Fällen und 1 unsicheren Fall halten sich die Lymphozytenzahlen innerhalb dieser Grenzen, aber die Abweichungen nach oben und unten sind bei dem grössten Teil so gering, dass die Lymphozytenzahl bei ihnen praktisch normal bleibt. In keinem Fall ist die Zunahme der Lymphozyten so gross, dass die Leukozytose des Patienten davon herrühren könnte, vielmehr ist die Leukozytose immer hauptsächlich oder ganz durch die Erhöhung der Zahl der myeloischen Zellen hervorgerufen.

Jugendformen der neutrophilen Leukozyten kamen im Blute in 5 sicheren Fällen vor, und ihre Zahl belief sich in den verschiedenen Fällen auf 0.2—2.5 %. Neutrophile Myelozyten wiederum fan-

Tabelle 2.

	Leukozyten	Lymphozyten- prozent	Absolute Zahl der Lymphozyten
1	9,400—17,500	5.4— 8.0	583—1,400
2	3,300—12,900	4.6—27.5	354—2,625
3	10,760—16,300	5.2—12.7	559—1,695
4	8,300—16,000	16.0—32.0	1,503—5,120
5	13,800—19,200	5.4— 9.3	929—1,786
6	9,300—12,000	9.5	1,140
7	5,100—12,300	8.5—29.4	766—2,117
8	6,100— 8,600	18.5—25.6	1,385—1,952
9	5,900— 8,500	17.0—25.3	1,367—1,543
10	3,300—18,900	4.5—21.5	286—2,873
11	6,800—13,300	17.0—20.0	1,360—1,598
12	6,300— 9,900	21.5—32.0	1,462—2,816
13	9,700—13,100	19.0—27.0	1,843—3,537
14	6,300— 9,500	14.0—19.0	1,302—1,767
15	10,000—49,900	1.0—28.5	357—7,235
16	5,600—11,850	17.2—25.4	1,930—2,038
17	6,400— 9,150	11.5—18.5	736—1,693
18	11,200	11.6	1,299
19	8,900	11.5	1,824
20	6,400—11,200	15.5—15.5	992—2,800
21	6,100— 6,100	42.0	2,226
22	5,650— 9,550	12.3—31.8	886—3,021
23	9,400—11,400	9.5—16.5	1,083—1,628
24	10,500		
25	19,200	5.0	960
26	16,200	15.5	2,511
27	11,400—13,100	15.5	2,031
28	5,000— 8,600	23.0—40.5	1,840—2,924
29	5,100—10,000	32.5	2,892
30	3,600— 7,800	33.0	2,013
31	7,500	15.5	1,163
32	6,300		
33	5,900—11,900	12.0—16.5	792—1,487
34	6,600— 7,200	37.5—40.5	2,475—2,916
35	6,100— 7,700	24.5—27.0	1,647—1,886
36	7,800—10,100	23.5—31.5	1,833—3,192
37	7,100— 8,000	34.5—42.0	2,553—3,360
38	3,400— 5,200	33.5—42.0	1,139—2,184
39	6,000— 6,200	37.0	2,220
40	6,600	31.5	2,079
41	9,200	38.0	3,496

den sich im Blute in 7 sicheren Fällen, wobei ihre Menge 0.2—37.0 % betrug. Grosse prozentuale Mengen wiesen nur 2 Patienten auf, deren Krankheitsbild gegen Ende der Krankheit an typische myeloische Leukämie erinnerte. Von diesen Fällen abgesehen, war das höchste Myelozytenprozent 1.5. Der eine der beiden erwähnten Fälle hatte ausserdem 1.5 % Myeloblasten im Blute. In den unsicheren Fällen wurden keinmal Jugendformen der weissen Blutkörperchen angetroffen.

Nach Ringoen finden sich im Blute eosinophile Zellen zu 2—4 % und basophile nach Michels, Abbott, Alder und Arneth zu 0.35—0.45 %. Diese Zahlen stimmen gut zu der gewöhnlichen klinischen Praxis, nach der angenommen wird, dass Eosinophilie oder Basophilie vorliegt, wenn die Zahl der eosinophilen Zellen 4 % und die der basophilen 0.5 % übersteigt. Eine leichte Eosinophilie ist in diesem Sinne in meinem Material recht gewöhnlich, denn da überschritt die Zahl der Eosinophilen 4 % in 13 sicheren Fällen, wobei die Werte in den verschiedenen Fällen zwischen 4.4 und 8.5 % schwankten, und in 3 unsicheren Fällen, in denen sich die Zahl der Eosinophilen auf 5.0—5.5 % belief. Die Zahl der Basophilen überstieg 0.5 % in 11 sicheren Fällen bei Werten zwischen 0.8 und 4.5 %. Von diesen ging jedoch das Prozent der Basophilen über 1 % nur in 6 Fällen hinaus, und die höchsten Werte, 3.2 und 4.5 %, wurden in den früher erwähnten 2 Fällen festgestellt, deren Krankheitsbild allmählich zu einer typischen myeloischen Leukämie wurde.

In der Blutungs- und der Gerinnungszeit sind nach der Literatur bei Polycythaemia essentialis keine Veränderungen zu finden, und auch ich habe in meinem Material diesbezüglich keine Abweichungen von den normalen Zeiten notiert.

Die Zahl der Thrombozyten ist nach Harrop und Wintrobe oft erhöht und kann manchmal das Drei- bis Vierfache der normalen Menge erreichen. Bei der Schätzung der Thrombozytenzahl muss man sich erinnern, dass die normalen Werte bei den verschiedenen Bestimmungsverfahren recht beträchtlich variieren. Bei der direkten Zählung der Thrombozyten, die bei ihrer Feststellung für die Patienten meines Materials zur Anwendung gekommen ist, beträgt die Zahl der Thrombozyten 200,000—400,000. In meinem Material wurden die Thrombozyten für 14 sichere und 4 unsichere Fälle berechnet. Nur die Werte für 4 sichere und 2 unsichere Fälle

beliefen sich auf 200,000—400,000. In 4 sicheren Fällen überstieg die Thrombozytenzahl nur etwas 400,000 und war 410,000—460,000, bei 3 fand sich eine deutlich erhöhte Thrombozytenzahl, die zwischen 600,000 und 750,000 schwankte, in 2 ging sie nur ein wenig unter 200,000, d. h. auf 157,000—187,000, herab, und in einem sicheren Fall wurde eine deutliche Thrombopenie konstatiert. Bei diesem Patienten wurde die Zählung der Thrombozyten viermal ausgeführt, und bei den verschiedenen Berechnungen ergaben sich folgende Werte: 31,000, 24,000, 98,000 und 143,000. Es kann sich also nicht um einen technischen Fehler gehandelt haben, sondern der Patient hatte wirklich eine deutliche Thrombopenie, die während der Behandlung allmählich verschwand. Es waren bei ihm weder Blutungen noch Zeichen einer hämorrhagischen Diathese zu bemerken. Im Schrifttum habe ich keine Angaben über Thrombopenie bei Polycythaemia essentialis gefunden. In den unsicheren Fällen wurde ausser den bereits erwähnten zwei normalen Thrombozytenzahlen in 1 Fall eine deutlich erhöhte Thrombozytenzahl, 732,000, und in einem anderen Fall eine nur etwas unter 200,000 herabgehende Zahl, 160,000, festgestellt.

Gutzeit und Minot und Buckman haben die Resistenz der roten Blutkörperchen bei Polycythaemia essentialis untersucht und beobachtet, dass eine totale Hämolyse meistens erst bei schwächeren Verdünnungen als gewöhnlich stattfindet, dass aber eine beginnende Hämolyse, die nur selten später als gewöhnlich erfolgte, oft schon früher als gewöhnlich, also in konzentrierteren Kochsalzlösungen als gewöhnlich eintrat. So würden nach ihren Beobachtungen bei Polycythaemia essentialis sowohl ungewöhnlich mehr als ungewöhnlich weniger resistente Erythrozyten im Blute zu finden sein, und dies würde, wie sie vermuten, darauf beruhen, dass das Alter der Erythrozyten mehr als gewöhnlich variiert. In meinen Fällen ist nur selten eine Bestimmung der Resistenz der roten Blutkörperchen ausgeführt worden, und bei diesen Bestimmungen wurde keine Abweichung von den normalen Werten gefunden.

Der Zerfall der Blutkörperchen ist bei Polycythaemia essentialis nicht gehemmt. Bei der Krankheit findet man im Gegenteil gewöhnlich einen erhöhten Ikterusindex, und Türk, Lommel, Minot und Buckman sowie Zadek haben auch Urobilinurie und Urobilino-genurie und Zadek und Pasehki und Diamant eine vermehrte

Sterkobilinmenge in den Fäzes nachgewiesen. Diese erhöhten Werte erklären sich wenigstens teilweise durch die im Verhältnis zur Norm viel grössere Zahl der roten Blutkörperchen, wobei selbstverständlich auch in der Zeiteinheit zerfallende Zellen in grösserer Menge vorhanden sind.

In meinem Material wurde der Ikterusindex nach Meulengracht in 10 sicheren Fällen bestimmt, und er war in allen diesen erhöht, mit Werten zwischen 1: 8 und 1: 27. In den unsicheren Fällen wurde er bei 2 Patienten festgestellt, und da war er bei dem einen erhöht, 1: 12, und bei dem anderen normal, 1: 5. Der Urobilinurie ist in meinem Material so selten Aufmerksamkeit zugewandt worden, dass sich daraus keine Schlüsse ziehen lassen.

Die Viskosität des Blutes ist bei Polyeythaemia essentialis stark erhöht und die Senkungsreaktion der Blutkörperchen herabgesetzt. Die letztere ist im allgemeinen während der ersten Stunde 0 oder liegt wenigstens unter 1 mm.

Die Viskosität ist in meinem Material nicht untersucht worden. Die Senkungsreaktion dagegen wurde, von 2 sicheren Fällen abgesehen, bei jedem Patienten mindestens einmal bestimmt. In den sicheren Fällen war der Wert der ersten Stunde bei 17 Patienten 0 und bei 2 ausserdem unter 1 mm. In 9 sicheren Fällen betrug die Senkung während der ersten Stunde mindestens 1 mm, wobei die Werte von 1—14 mm variierten. In allen letztgenannten Fällen war die Zahl der roten Blutkörperchen unter 7.5 Millionen. Der höchste Wert, 14 mm, trat bei einem Patienten nach Magenresektion auf. Der nächsthöchste Wert, 8 mm, fand sich unter ebenfalls abnormen Verhältnissen bei einem Patienten, der überall im Körper Thrombosen hatte und in agone in das Krankenhaus gebracht worden war. In den übrigen 7 Fällen betrug die Senkung 2 mal 1 mm und 3 mal 2 mm während der ersten Stunde. Bei dem einen der Patienten, deren Krankheitsbild allmählich in Leukämie überging, wurde die Senkungsreaktion erst im leukämischen Stadium bestimmt, als der Patient schon Anämie hatte, so dass sie nichts über die bei Polycythaemia essentialis auftretende Senkungsreaktion aussagt. Übrig ist der allerleichteste Fall, eine Frau, bei der die Erythrozytenzahl 5.45 Millionen war. Ihre Senkungsreaktion war während der ersten Stunde 5 mm. In den unsicheren Fällen betrug die Senkungsreaktion während der ersten Stunde in 2 Fällen 0, in 2 1 mm, in 6 1.5—3 mm und in 1 4.5 mm. In 12 siehe-

ren Fällen war der Wert der Senkungsreaktion auch während der zweiten Stunde 0. Von den erwähnten Ausnahmen abgesehen, war der Wert der zweiten Stunde in den übrigen sicheren Fällen und mit 3 Ausnahmen auch in den unsicheren unter 10 mm.

Mehrere Forscher haben festgestellt, dass auch die Menge des Blutplasmas bei Polycythaemia essentialis beträchtlich vermehrt ist. Bei meinem Material sind keinmal Bestimmungen des Blutplasmas ausgeführt worden.

Grafe, Abbott, March, Isaacs, Minot und Buekman, Brown und Giffin, Harrop und Bliss sowie R. Ehrström haben konstatiert, dass der Grundumsatz bei Polycythaemia essentialis oft leicht erhöht ist. Nur Zadek hat einen Fall veröffentlicht, in dem sich an die Polycythaemia essentialis eine deutliche Thyreotoxikose anschliesst.

Mein Material enthält einen Fall, der eine grosse Struma, eine deutliche Thyreotoxikose und eine subjektiv symptomlose Polycythaemia essentialis hatte, trotzdem die Erythrozytenzahl hier den beachtlichen Betrag von 7.03 Millionen zeigte. Der Grundumsatz der Patientin war + 43 %. In 14 anderen Fällen wurde ein Grundumsatzversuch ausgeführt. Dabei wurde konstatiert, dass der Grundumsatz in 6 Fällen normal, in 7 bei Werten zwischen + 17 und + 46 % erhöht und in einem herabgesetzt, — 15 %, war. Auch in 3 unsicheren Fällen fand ein Grundumsatzversuch statt, dessen Ergebnis in 1 Fall normal, in 1 erhöht, + 17 %, und in 1 herabgesetzt, — 14 %, war.

Bezüglich der Menge des Serumkalziums sind die Forscher zu stark abweichenden Resultaten gekommen. So stellten Brown und Roth und Albreeht und Reinwein in ihren meisten Fällen einen erhöhten Serumkalziumgehalt fest, Benedict und Turner sowie Harrop und Wintrobe dagegen fanden bei ihren Untersuchungen das Serumkalzium normal. Über die normale obere Grenze des Serumkalziums sind die verschiedenen Forscher etwas geteilter Meinung, indem die einen 11 mg % als diese Grenze betrachten, aber wenigstens über 12 mg % steigende Werte dürften sicher als erhöht aufzufassen sein.

In meinem Material wurde das Serumkalzium in 11 sicheren Fällen bestimmt, und es war da in 5 bei Werten zwischen 9.9 und 12.0 mg % normal, während in 6 eine deutlich erhöhte Serumkalziummenge mit Werten zwischen 12.9 und 16.0 mg % konstatiert wurde. Auch in 2 unsicheren Fällen wurde der Serumkalziumgehalt ermittelt und in dem einen normal, 9.0 mg %, und in dem anderen deutlich erhöht, 14.0 mg %, gefunden.



Die Therapie der Polycythaemia essentialis ist, da man die Ätiologie der Krankheit nicht kennt, rein symptomatisch. Es sind mehrere Behandlungsmethoden mitgeteilt worden, aber sie alle gehen prinzipiell darauf aus, entweder die Zahl der Erythrozyten und möglicherweise auch der anderen im Übermass vorhandenen Blutkörperchen herabzudrücken oder auf die eine oder andere Weise eine übermässige Blutbildung zu verhindern. Bei der Beurteilung der Behandlungsergebnisse muss man sich stets vergegenwärtigen, dass Spontanremissionen bei Polycythaemia essentialis recht gewöhnlich sind, weshalb eine zufällige Abnahme der Erythrozytenzahl nicht immer von der angewandten Methode herzurühren braucht. Aus diesem Grunde können sichere Schlüsse nur aus grossen homogenen Materialien gezogen werden, die aber andererseits wegen der Seltenheit der Krankheit schwer zusammenzubringen sind. Mit allen angewandten Verfahren ist im allgemeinen nur eine gelegentliche Besserung sowohl in bezug auf die von der Krankheit ausgelösten Symptome als auch auf die Zahl der roten Blutkörperchen erzielt worden, und nur in wenigen Fällen hat die Behandlung für längere Zeit Nutzen gestiftet.

Zur Vernichtung der Blutkörperchen oder zur Beförderung ihres Zerfalles sind Venäsektionen und folgende Medikamente benutzt worden: Fowlers Lösung und andere Arsenikpräparate, Milzpräparate und Milz als solche, Benzol und Phenylhydrazin. In einem meiner Fälle habe ich ausserdem zu diesem Zweck Fiebertherapie angewandt, die, soviel ich sehen kann, früher nicht zur Behandlung der Polycythaemia essentialis herangezogen worden ist. Um die Vermehrung der Blutkörperchen zu verhindern, sind Diät, Röntgentherapie und Magenresektionen zur Verwendung gekommen.

Bei meinem Material sind Milz und Milzpräparate, Phenylhydrazin, Venäsektionen, Fiebertherapie, Röntgenbehandlung und Magenresektionen benutzt worden.

Milz wurde während des Krankenhausaufenthaltes 5 Patienten gegeben, wonach einige Patienten sie in den Pausen der Behandlung zu Hause eingenommen haben. Bei 1 Patienten sank die Erythrozytenzahl während der Milztherapie um 0.73 Millionen, bei einem anderen um 0.38 Millionen, stieg aber bei 2 etwas und bei einem dritten um 0.58 Millionen. Mein Material ist in dieser Beziehung klein, aber es spricht doch dafür, dass Milz in der Therapie der Polycythaemia essentialis kaum von Bedeutung ist.

Phenylhydrazin hat nur 1 Patient bekommen. Bei diesem sank die Zahl der roten Blutkörperchen um 0.44 Millionen und das Hämoglobin um 15 Sahli-Einheiten. Ryle, Winterfeld, Engel und mehrere andere Autoren haben gute Ergebnisse der Phenylhydrazinbehandlung gemeldet. Auch der Fall meines Materials zeigt ein verhältnismässig gutes Resultat. Bei der Verabreichung des Phenylhydrazins muss man sich nur vor einer Überdosierung hüten, denn dabei kann infolge eines übermässigen Zerfalls der Blutkörperchen eine schwierige Situation entstehen. Einen solchen Zustand hat u. a. Hoecker beschrieben. Die Tagesdosis sollte nach Engel 0.1 g nicht überschreiten, und nach einwöchiger Behandlung sollte eine mindestens 10tägige Pause eingeschoben werden.

Venäsektionen wurden bei 11 Patienten meines Materials ausgeführt. Bei einem (Fall 7) wurden sie in mehreren Serien angewandt. Ich gebe die mit den Venäsektionen erreichten Resultate in Tabelle 3 wieder. Wie man aus der Tabelle ersieht, ist die Verminderung der Erythrozyten auf keine Weise proportional der entnommenen Blutmenge oder der Zahl der Entnahmen, so dass die Ergebnisse offenbar in hohem Grade durch spontane Variationen beeinflusst worden sein müssen. Nach derselben Richtung weist auch die Tatsache, dass die Erythrozytenzahl in 3 und der

Tabelle 3.

Nummer des Falles	Zahl der ausgeführten Venäsektionen	Entnommene Blutmenge ml	Veränderung der Erythrozytenzahl Mill.
1	6	2,500	—1.23
3	5	485	+0.01
5	1	175	—0.93
6	3	1,410	—1.67
7	1	300	—0.20
7	4	1,850	—0.20
7	1	500	—0.70
7	3	1,250	+0.17
9	2	520	+0.79
10	1	250	—0.32
23	4	900	—0.23
26	2	800	—1.50
28	2	700	—0.05
32	1	450	—0.73

Hämoglobinwert in 5 Fällen erhöht sind. Das Ergebnis spricht jedoch meines Erachtens dafür, dass die Venäsektionen bei der Behandlung der Polycythaemia essentialis meist von recht günstiger Wirkung sind.

Wie ich oben erwähnte, habe ich bei 1 Patienten Fiebertherapie angewandt, da ich bei der Durchmusterung meines Materials fast in allen Fällen, in denen der an Polycythaemia essentialis leidende Patient aus der einen oder anderen Ursache Fieber hatte, die Feststellung machte, dass die Zahl der roten Blutkörperchen regelmässig während des Fiebers sank. Ich habe nicht konstatieren können, dass dieses Verfahren früher im Schrifttum bei der Behandlung der Polycythaemia essentialis empfohlen worden wäre. Mein Patient bekam 5 Milchinjektionen von 2 ml an, und die Menge der injizierten Milch wurde jedesmal um 2 ml erhöht. Nach 5 Injektionen war die Erythrozytenzahl des Patienten um 1.39 Millionen und das Hämoglobin um 7 Sahli-Einheiten gesunken. Die Fiebertherapie scheint also in manchen Fällen mindestens eine ebenso günstige Wirkung zu haben wie andere blutzeretzende Behandlungsverfahren.

Röntgentherapie wurde bei meinem Material am allerrhäufigsten angewandt. Die Beurteilung der Behandlungsergebnisse wird in diesen Fällen dadurch erschwert, dass die Therapie in den verschiedenen Fällen auf verschiedene Stellen des Körpers und ausserdem nach verschiedener Technik appliziert worden ist. Im Hinblick hierauf muss man sich mit einem ganz allgemeinen Urteil begnügen. Die Therapie wurde im ganzen 11 Patienten gegeben. Bei 4 sank die Zahl der roten Blutkörperchen deutlich nach allen Applikationen. Ebenfalls bei 4 wurde nach den einen Applikationen eine Abnahme, nach den anderen dagegen eine Zunahme der Erythrozytenzahl beobachtet. Bei 3 Patienten wuchs die Zahl der roten Blutkörperchen nach allen Röntgenapplikationen an. Je nach der verschiedenartigen Applikation kann man meines Erachtens auf Grund meines Materials nur sagen, dass die Röntgentherapie nicht auf alle Patienten günstig zu wirken scheint, während sie bei geeigneter Technik in manchen Fällen offenbar ein gutes Resultat gibt.

Einer Magenresektion wurden 3 Patientinnen meines Materials unterworfen. Dieselben Fälle hat R. Ehrström in einer Zusammenkunft des Ärztevereins Finnlands besprochen. Eine der Pati-

entinnen, die auch Magenzirrhose hatte, starb sofort nach der Operation. Die beiden anderen erholten sich gut von dem Eingriff. Seit der Operation beider sind jetzt 4 Jahre vergangen. Die eine dieser operierten Patientinnen habe ich nicht angetroffen, die andere teilt mit, dass ihr Befinden seit der Operation die ganze Zeit ausgezeichnet gewesen ist. Der Kopfschmerz und der Schwindel, wovon die Patientin vor der Operation heimgesucht war, sind verschwunden, und sie hat nach der Operation keine Behandlung gebraucht, während sie vorher mehrere Jahre wiederholt im Krankenhaus gewesen ist. Eine Blutuntersuchung konnte ich bei ihr jetzt nach der Operation nicht ausführen. In geeigneten Fällen scheint also die Magenresektion einen sehr günstigen Einfluss auf die bei Polycythaemia essentialis auftretenden Beschwerden auszuüben. Die Anwendung der Behandlungsmethode in grösserem Massstabe wird nur durch die aussergewöhnlich grosse Operationssterblichkeit, die auf der grossen Blutungs- und Thrombosedisposition der Patienten beruht, erschwert.

Der mit Phenylhydrazin behandelte Patient gehört zu den unsicheren Fällen, ebenso ein Patient, bei dem Venäsektionen ausgeführt wurden. Die anderen unsicheren Fälle erhielten keine unmittelbar auf die Polyzythämie gerichtete Therapie.

Die Polycythaemia essentialis ist eine sich langsam entwickelnde chronische Krankheit, was n. a. daraus ersichtlich wird, dass mancher Patient jahrelang, ja über 10 Jahre, Beschwerden gehabt hat, bevor er sich in ärztliche Behandlung begab. Die Krankheit bedroht das Leben der Patienten vor allem durch ihre Komplikationen und dadurch, dass die von Polycythaemia essentialis Befallenen viel schlechter als der gesunde Mensch Infektionskrankheiten überstehen.

Von den 30 sicheren Patienten meines Materials starben 6 im Krankenhaus. Die Todesursache war in 3 Fällen eine auf Grund einer Thrombose entwickelte Apoplexie, in 1 eine Infektio acuta, in 1 Bronchopneumonie, und eine Patientin ging bei der an ihr ausgeführten Magenresektion verloren.

Die Polycythaemia essentialis steht augenscheinlich in einem Zusammenhang mit der myeloiden Leukämie. Ein Beweis dafür ist, dass im Schrifttum 10 Fälle (Blumenthal, Hedenius, Zimmermann, Rosin, Minot und Backman, Daniels und von Buchem, Mc Alpin, Herxheimer, Jung und Brieger und Forschbach) mit-

geteilt worden sind, in denen eine typische Polycythaemia essentialis im Endstadium der Krankheit in eine myeloische Leukämie übergang. In mehreren Fällen konnten typische Symptome der myeloischen Leukämie festgestellt werden, vor allem war das leukoblastische Gewebe im Knochenmark deutlich reichlicher als das erythroblastische. Nur Ghiron hat einen Fall veröffentlicht, in dem eine typische myeloische Leukämie sich allmählich in eine typische Polycythaemia essentialis verwandelte. In seinem Fall stieg die Zahl der roten Blutkörperchen von 2.1 auf 7.2 Millionen, und zugleich wurde das Gesicht des Patienten typisch rot. Diese Beziehung der myeloischen Leukämie zu der Polycythaemia essentialis ist noch völlig unklar.

Seuderling hat 2 vom Gewöhnlichen abweichende Polyzythämiefälle veröffentlicht. In dem einen wurde anfangs eine Anämie und Leukozytose beobachtet, später verwandelte sich die Anämie, die sich als eine Blutungsanämie erwies, in eine Polyzythämie. Der andere Fall begann mit den Symptomen einer recht typischen chronischen myeloischen Leukämie, ging aber nach und nach in eine ausgeprägte Polyzythämie über. Im Endstadium verschwand die Polyzythämie, und der Fall nahm vor dem Tode wieder in hohem Grade den Charakter einer myeloischen Leukämie an, obwohl Seuderling in seiner Arbeit diese letzterwähnte Veränderung des Krankheitsbildes nicht beachtet hat. Dieser Fall ist in mein Material aufgenommen (Fall 10).

Andere Fälle dieser Art, in denen die Krankheit als myeloische Leukämie angefangen hätte, zwischendurch zu einer Polycythaemia essentialis und dann von neuem zu einer myeloischen Leukämie geworden wäre, sind früher nicht veröffentlicht worden.

Da mein Material ausserdem einen Fall enthält, in dem die Krankheit mit den Symptomen einer typischen chronischen myeloischen Leukämie begann, allmählich in eine typische Polycythaemia essentialis und einige Zeit danach wieder in eine sogar deutlicher als das Anfangsstadium ausgeprägte myeloische Leukämie übergang, teile ich den Krankenbericht dieses Falles in den Hauptzügen mit. In demselben Zusammenhang gebe ich aus meinem Material den wesentlichen Zügen nach die Krankheitsgeschichte eines Falles, in dem die Polycythaemia essentialis mit Thyreotoxikose verknüpft ist, und eines Falles, in dem der Patient zugleich mit Polycythaemia essentialis einen Nebennieren-

tumor hatte. Im Schrifttum sind früher nur ein Fall von Polycythaemia essentialis in Verbindung mit Thyreotoxikose und 10 Fälle im Zusammenhang mit Nebennierentumor vorgeführt worden.

Fall 15. H. A., 53jährige Restaurantgehilfin. Anamn.: Vor 9 Jahren wurde bei der Patientin eine Geschwulst aus dem Bauche geschnitten, und nach der Operation blieben die Menstruationen weg. Vor 4 Jahren bemerkte die Patientin einen Knoten unterhalb des linken Rippenbogens, ihre Haut wurde gelblich, und sie wurde müde. Sie nahm 31 kg ab. Ein halbes Jahr heftiger Kopfschmerz. St. pr.: 14. III. 35. Haut gelblich braun, im Gesicht reichliche Pigmentation. Die sichtbaren Schleimhäute blass. Herz sowohl nach rechts als nach links erweitert. Systolisches Geräusch an der Spitze. Milz etwa einen Handteller und Leber 2 Fingerbreit unterhalb des Rippenbogens; beide etwas empfindlich. Blutbild 15. III. 35. Hb 57 Sahli. E. 4.45 Millionen. Leukozyten 36,600. Bekam eine Ziemssen-Kur und Röntgen auf die Milz. 2. VII. 35. Hb 85 Sahli. E. 6.64 Millionen. L. 49,600. Im Blute 0.2 % neutrophile Myelozyten. Bekam Röntgentherapie auf die langen Knochen und Milz per os. 29. X. 35. Hb 85 Sahli. E. 7.25 Millionen. L. 35,000. 28. I. 36. Hb 80 Sahli. E. 6.29 Millionen. L. 17,300. Im Blute neutrophile Myelozyten 7.5 %. 8. II. 36. Hb 75 Sahli. E. 5.86 Millionen. L. 27,900. Im Blute neutrophile Myelozyten 37.0 % und Normoblasten 2: 200. 17. I. 36. Hb 68 Sahli. E. 5.02 Millionen. L. 49,900. Im Blute neutrophile Myelozyten 23.5 % und Normoblasten 2: 200. 25. II. 36. Hb 50 Sahli. E. 3.55 Millionen. L. 30,700. Im Blute 32.5 % neutrophile Myelozyten und 2: 200 Normoblasten. An demselben Tage traten im Gesicht der Patientin typische leukämische Infiltrate auf, und am folgenden Tage starb sie. D.: Anfangs Leucaemia myeloica? Später Polycythaemia essentialis. Schliesslich Leucaemia myeloica. Obduktionsdiagnose: Pneumoniae lobulares pulm. dx. Hypertrophia et dilatatio cordis. Hyperplasia lienis et hepatis. Infarctus lienis.

Fall 21. J. F., 47jährige Frau eines Kleinbauern. Anamn.: 12 Partus. Im Zusammenhang mit den Graviditäten entstanden bei der Patientin Phlebektasien, und auf Grund derselben entwickelte sich am Unterschenkel ein Geschwür, das mehrmals offen gewesen ist. Im Frühjahr 1937 wurde in einem Augenlid Krebs festgestellt und dieser mit Radium behandelt. Vor 10 Jahren bemerkte die Patientin, dass ihre Schilddrüse sich zu vergrössern begann, während der 2—3 letzten Jahre wuchs diese schneller. Ein Jahr lang hatte die Patientin Herzklopfen, Atemnot, dyspeptische Beschwerden und Schlaflosigkeit. Mit der Zeit ist sie immer nervöser geworden. St. pr.: Subkutis stark reduziert. Lippen intensiv gerötet. Umgebung des Mundes, Fingerspitzen und besonders die Nägel rot. Grosse knotige Struma. Leicht feinschlägiger Tremor in den Fingern. Keine Augensymptome. Reflexe gewöhnlich. A. radialis hart, geschlängelt, Puls unregelmässig und ungleichmässig, 75—85/Min. Herz sowohl nach rechts als nach links erweitert, systolisches Geräusch am besten in der Gegend der Spitze hörbar. Herztöne stark dröhnend. Pulsdefizit 60—70. Blutdruck 130/90. Milz perkussorisch vielleicht ein wenig vergrössert. Grundum-

satzversuch + 43 %. Blutbild: Hb 120—125 Sahli. E. 6.52—7.03 Millionen. L. 5,100—6,100. D.: Struma nodosa. Thyreotoxycosis. Myodegeneratio cordis. Polycythaemia essentialis.

Fall 27. K. I., 38jährige Näherin. Anamn.: Mit 8 Jahren hatte die Patientin Osteomyelitis im Bein, und es wurde bei ihr eine Resectio coxae ausgeführt. Sonst früher gesund. Die Menses begannen, als die Patientin 17 Jahre alt war, und sind regelmässig gewesen, Dauer 3 Tage, Zyklus 4 Wochen. Vor 1  $\frac{1}{2}$  Jahren begann die Patientin Fett anzusetzen und hat seitdem 6 kg zugenommen. Im Äusseren ist sie allmählich immer stämmiger und maskuliner geworden. Vor 8 Monaten bemerkten die Bekannten, dass das Gesicht der Patientin röter als vorher geworden war, ebenso der Hals. In 7 Monaten ist ihr das Haar auf dem Kopfe stark ausgegangen, und vor 5 Monaten begannen der Patientin ein Schnurrbart und ein Backenbart zu wachsen. St. pr.: Macht einen ausgeprägt maskulinen Eindruck. Behaarung reichlicher als gewöhnlich. Feuchtigkeit der Haut erhöht. Hautfarbe im Gesicht und am Halse röter als normal, desgleichen die sichtbaren Schleimhäute dunkelrot. Herz sowohl nach rechts als nach links erweitert. Systolisches Geräusch. Milz perkussorisch vergrössert. Blutbild: Hb 110 Sahli. E. 6.16—6.48 Millionen. L. 11,400—13,000. Bekam während des Anstaltsaufenthaltes eine leichte Infektion, die in einigen Tagen zum Tode führte. D.: Tumor gl. suprarenalis. Polycythaemia essentialis. Acc. Infectio acuta. Obduktionsdiagnose: Tumor gl. suprarenalis sin. Hypertrophia cordis. Hyperplasia lienis. Hyperaemia organorum omnium. Concretio totalis pleurae sin. Atelectasis pulm. sin. Eburneatio femoris sin. Hyperplasia rubra medullae diaphyseos femoris dx.

### *Besprechung der Ergebnisse.*

Meine Fälle von Polycythaemia essentialis bilden eine bedeutend einheitlichere Krankheitsgruppe als die im ersten Teil meiner Arbeit vorgeführten Fälle von Polycythaemia symptomaticea. In der Gruppe meiner unsicheren Fälle treten einige ähnliche Züge wie in meinen Fällen von Polycythaemia symptomaticea auf, da in denselben aber keine sichere Ursache aufzufinden ist, für die man den Sauerstoffmangel in den Geweben und damit die Polycythaemia symptomaticea hätte verantwortlich machen können, habe ich sie als unsichere Fälle von Polycythaemia essentialis behandelt.

Das Alter der Patienten entspricht im allgemeinen dem Alter der Polycythaemia symptomaticea-Patienten, deren Grundkrankheit entweder ein erworbener Herzfehler oder ein Lungenemphysem war; während die Patienten mit einer Polyzithämie, die durch einen angeborenen Herzfehler verursacht ist, natürlicherweise

im allgemeinen jünger sind. Das Alter meiner unsicheren Fälle war etwas niedriger als das der sicheren.

Ein paar leichtere sichere Fälle von Polycythaemia essentialis ausgenommen, hatten alle sicheren Fälle durch Polyzythämie hervorgerufene Beschwerden, die dagegen nur jeder zweite unsichere Fall und nur ein paar meiner an Polycythaemia symptomatice leidenden Patienten aufwiesen. Blutungen waren sehr gewöhnlich in meinen sicheren Fällen von Polycythaemia essentialis, in den unsicheren kamen sie ebensowenig wie in den Fällen von Polycythaemia symptomatice vor. Thrombosen waren dagegen in allen Gruppen im Verhältnis gleich oft zu verzeichnen. Zum mindesten leichte innersekretorische Störungen wurden ebenfalls in allen Gruppen angetroffen.

Die Farbe der Haut war in allen meinen sicheren Fällen von Polycythaemia essentialis rot oder vorwiegend rot, und auch nur in 2 unsicheren Fällen wurde im Gesicht Zyanose festgestellt, die dagegen in allen meinen Fällen von Polycythaemia symptomatice ausser einem auftrat. Eine Erhöhung des Blutdruckes fand sich in allen Gruppen zu ungefähr demselben Betrag wie überhaupt bei Personen des in Rede stehenden Alters. Peripherische Arteriosklerose war dagegen bei den Patienten mit Polycythaemia essentialis deutlich gewöhnlicher als bei den anderen. Dyspeptische Beschwerden und Ulkus waren in allen Gruppen selten. Milzvergrößerung war in meinen Fällen von Polycythaemia essentialis gewöhnlich, fehlte aber doch in 35 %, wurde in sämtlichen Fällen von Polycythaemia symptomatice vermisst und war in den unsicheren Fällen von Polycythaemia essentialis recht selten.

Die Erythrozytenzahl entsprach in den Fällen von Polycythaemia essentialis ungefähr den bei angeborenen Herzfehlern konstatierten höchsten Polycythaemia symptomatice-Werten, ebenso die Hämoglobinemengen. Der Farbeindex, der in den Fällen von Polycythaemia symptomatice regelmässig normal war, war dagegen manchmal herabgesetzt, während besonders in einigen unsicheren Fällen auch ein leicht erhöhter Farbeindex gefunden wurde. Leukozytose, die in den Fällen von Polycythaemia symptomatice ein seltenes Symptom darstellte, war jetzt sehr gewöhnlich und kam in 67 % vor. Die Zunahme der weissen Blutkörperchen beruhte in beiden Krankheitsgruppen auf der Vermehrung der myeloischen Zellen. Jetzt wurden im Blute ab und zu Jugendformen



von roten sowie von weissen Blutkörperchen angetroffen, die in den Fällen von Polycythaemia symptomatica keinmal auftraten. Eosinophilie war in beiden Krankheitsgruppen verhältnismässig selten. Die Senkungsreaktion war in beiden Gruppen regelmässig sehr niedrig.

In der Therapie erwiesen sich die Venäsektionen nach meiner Auffassung am zuverlässigsten, in manchen Fällen auch die Röntgenbehandlung, die jedoch in einigen Fällen ganz unwirksam war. Phenylhydrazintherapie wurde nur in einem Fall angewandt, und da war das Ergebnis ein gutes. Hinsichtlich der von mir in Gebrauch genommenen Fiebertherapie lassen sich vorderhand keine Schlüsse ziehen, da sie nur bei einem Patienten versucht wurde, aber in diesem Fall entsprach das Ergebnis den besten mit Venäsektionen und Röntgenbehandlung erzielten Resultaten. Mit der Magenresektion wurde auch einmal ein gutes Resultat erzielt. Die Verallgemeinerung dieser Therapie ist jedoch vor allem wegen der grossen Thrombosedisposition der an Polycythaemia essentialis leidenden Patienten schwer, aber sie dürfte besonders in den Fällen in Betracht kommen können, in denen die Patienten zugleich mit Polyzythämie Ulkus haben.

### Zusammenfassung.

Das Material umfasst 30 sichere Fälle von Polycythaemia essentialis und 11 unsichere Fälle. Als sicher habe ich die Fälle betrachtet, in denen die Zahl der roten Blutkörperchen bei Männern 6.2 Millionen und bei Frauen 5.4 Millionen übersteigt. Als unsichere Fälle habe ich andererseits die männlichen Patienten angesehen, bei denen die Erythrozytenzahl 6.2—5.4 Millionen beträgt und die keine Krankheit haben, auf die eine symptomatische Polyzythämie hätte zurückgeführt werden können.

Zu dem Material gehören folgende selten im Schrifttum angeführten Krankheitskombinationen: 1 Fall von Polycythaemia essentialis in Verbindung mit Thyreotoxikose, 1 Fall von Polycythaemia essentialis bei Nebennierentumor und 1 Fall, in dem die Krankheit mit unbestimmten und leichten Symptomen von Leukämie begann, sich dann zu einer typischen Polycythaemia essentialis entwickelte und wieder als typische myeloische Leukämie endigte.

In den sicheren Fällen war das Verhältnis der Männer zu den Frauen 1.1:1, im ganzen Material 1.9:1. Die Fälle kamen zum

ersten Male mit 31—60 Jahren in Behandlung. Der jüngste Fall war eine 20jährige Frau. Die Dauer der Symptome schwankte vor der Behandlung ausserordentlich stark. Die häufigsten Symptome waren Kopfschmerz und Schwindel. Blutungen kamen in 13 Fällen vor. Thrombosen hatten 8 Fälle. Bei allen weiblichen Patienten, die beim Ausbruch der Krankheit noch nicht im Klimakteriumalter standen, trat entweder ein vollständiges Aufhören oder wenigstens eine deutliche Abnahme der Menstruationen ein.

Die Farbe der Haut war in den sicheren Fällen rot oder zeigte zum mindesten eine rote Nuance. In den unsicheren Fällen war sie bei 2 Patienten gewöhnlich und bei 2 zyanotisch, sonst rot oder rötlich. Das Herz war in 15 Fällen deutlich erweitert. Eine ausgeprägte peripherische Arteriosklerose kam in 14 Fällen vor, dazu in 5 eine Aortensklerose. 17 sichere Fälle hatten wenigstens zeitweise Hypertonie. Von den unsicheren Fällen wiesen im ganzen 4 Hypertonie auf. Dyspeptische Beschwerden traten in 2 sicheren Fällen auf, und ausserdem hatte einer Ulkus. Unter den unsicheren Fällen wurde bei den Patienten einmal Magenkrebs, einmal Dyspepsie und einmal Ulkus festgestellt. Die Milz war in 19 sicheren und 2 unsicheren Fällen vergrössert. 9 sichere und 2 unsichere Fälle hatten eine andauernde Albuminurie.

Die höchste Erythrozytenzahl lag in den sicheren Fällen zwischen 10.56 und 5.45 Millionen, in den unsicheren zwischen 6.15 und 5.52 Millionen, und der höchste Hämoglobinwert war in den sicheren Fällen 140—95 (Sahli) und in den unsicheren 123—95 (Sahli). Jugendformen der roten Blutkörperchen hatten nur 2 sichere Fälle im Blute. Eine deutliche Leukozytose trat in 20 sicheren und 2 unsicheren Fällen auf. Die Leukozytose beruhte hauptsächlich auf der Vermehrung der myeloischen Zellen. 8 sichere Fälle hatten Jugendformen der Leukozyten im Blute. Eosinophilie kam in 13 sicheren und 3 unsicheren Fällen vor, Basophilie in 11 sicheren Fällen, 3 sichere Fälle und 1 unsicherer hatten eine deutlich vermehrte Thrombozytenmenge im Blute, 1 sicherer Fall dagegen eine deutliche Thrombopenie. Der Ikterusindex nach Meulengraecht war, von einem unsicheren Fall abgesehen, in allen Fällen, in denen er bestimmt wurde, erhöht. Der Wert der Senkungsreaktion während der ersten Stunde war 0 mm in 17 sicheren und 2 unsicheren Fällen, ausserdem lag er in 2 sicheren Fällen unter 1 mm. Die höchsten Werte der Senkungsreaktion während

der ersten Stunde waren in den unkomplizierten sicheren Fällen bei 3 Patienten 2 mm und in einem, dem allerleichtesten Fall 5 mm.

Der Grundumsatzversuch zeigte deutlich erhöhte Werte in 7 sicheren Fällen und 1 unsicheren Fall und herabgesetzte Werte in 1 unsicheren Fall. In 6 sicheren Fällen und 1 unsicheren Fall wurde ein erhöhter Kalziumgehalt des Serums beobachtet.

Bei der Behandlung wurden die besten Ergebnisse mit Venäsektionen und in einigen Fällen mit Röntgentherapie erreicht. Ein Fall wurde nach Magenresektion subjektiv symptomlos, und Phenylhydrazin hatte in dem einzigen Fall, in dem es angewandt wurde, eine gute Wirkung. Als neues Behandlungsverfahren ist die Fiebertherapie vorgeführt, die jedoch bisher nur bei einem Patienten und zwar mit Erfolg zur Verwendung gekommen ist.

6 Patienten starben während ihres Aufenthalts im Krankenhaus. Die Todesursache war in 3 Fällen eine auf Grund einer Thrombose entwickelte Apoplexie, in 1 eine Infectio acuta, in 1 Bronchopneumonie, und in 1 Fall trat der Tod im Zusammenhang mit einer Magenresektion ein.

### Schrifttum.

- Abbott, E. M.: Ref. nach Harrop und Wintrobe. — Albrecht und Reinwein, H.: Klin. Wschr. 1930: 9: 1964. — Alder, A.: Fol. haemat. Archiv. 1923: 28: 249. — Arneth, F.: Berl. klin. Wschr. 1920: 57: 109. — Bauer, J.: Die konstitutionelle Disposition zu inneren Krankheiten. Berlin 1921. — Barath, E. und Fülöp, J.: Z. klin. Med. 1935: 129: 172. — Benedict, E. M. und Turner, K. B.: J. clin. Invest. 1939: 9: 263. — Bingel, A.: Dtsch. med. Wschr. 1924: 50: 330. — Blad, A.: Fol. haemat. Archiv. 1905, 2: 685. — Bliss, T. L.: Ref. nach Harrop und Wintrobe. — Bloom, William: Handbook of Hematology 1938: 1: 373. — Blumenthal, R.: Bull. Acad. Belg. 1905: 19: 775. — Derselbe: Arch. Méd. expér. et d'Anat. path. 1907: 19: 697. — Boyd, W.: Am. J. med. Sci. 1934: 187: 589. — Brieger, H. und Forscbach, J.: Klin. Wschr. 1922: 7: 845. — Brown, G. E. und Giffin, H. Z.: Am. J. med. Sci. 1926: 171: 157. — Dieselben: Arch. int. Med. 1930: 46: 705. — Brown, G. E. und Roth, G. M.: J. clin. Invest. 1929: 6: 159. — Cautley, E.: Lancet. 1908: 1: 1204. — Chace: Ref. nach Harrop und Wintrobe. — Daniels, L. P. und v. Buchem, F. S. P.: Klin. Wschr. 1928: 7: 121. — Del Baere, L. J.: Wien. Arch. inn. Med. 1926: 12: 593. — Doll, H. und Rotschild, K.: Klin. Wschr. 1922: 1: 2580. — Douglas, J. und Eisenbrey, A. B.: Am. J. med. Sci. 1914: 146: 479. — Ehrström, R.: Nord. Med. 1939: 2: 1760. — Derselbe: Nord. med. Tskr. 1932: 4: 685. — Engel, M.: Med. Klin. 1931: 21: 1603. — Engelking, E.: Dtsch. med. Wschr. 1920: 46: 1140. — Fletcher, T. B.: Ref. nach Harrop und Wintrobe.

- Gaisböck, F.: *Erg. inn. Med.* 1922: 21: 210. — Ghiron, M.: *Fol. haemat. Z.org.* 1925: 22: 135. — Grafe, E.: *Ref. nach Harrop und Wintrobe.* — Günther, H.: *Dtsch. Arch. klin. Med.* 1929: 165: 41. — Gutzeit, K.: *Dtsch. Arch. klin. Med.* 1920: 141: 30. — Halbertsma, I.: *Am. J. Dis. Childr.* 1933: 46: 1356. — Hann, R. G.: *Lancet.* 1908: 1: 160. — Harrop, Jr., George, A. und Wintrobe, Maxwell, M.: *Handbook of Hematology.* 1938: 4: 2361. — Hedenius: *Fol. haemat. Z.org.* 1914: 15: 203. — Herxheimer, G.: *Berl. klin. Wschr.* 1913: 50: 1458. — Hess, L.: *Ref. nach Harrop und Wintrobe.* — Hiltzenberger, K.: *Klin. Wschr.* 1934: 13: 1345. — Hoecker, H.: *Klin. Wschr.* 1932: 11: 745. — Hollaender, L.: *Wien. Arch. inn. Med.* 1925: 10: 283. — Isaacs, R.: *Fol. haemat. Z.org.* 1922: 22: 134. — Jedwabnik, David: *Drei Fälle von Polycythaemia rubra megalosplenica.* Thesis. Berlin 1913. — Jung, K.: *Ref. nach Harrop und Wintrobe.* — v. Korányi, A.: *Ref. nach Harrop und Wintrobe.* — Lederer, K.: *Wien. Arch. inn. Med.* 1923: 5: 23. — Leon-Kindberg, M. und Garcin, R.: *Ref. nach Harrop und Wintrobe.* — Lichtwitz, L.: *Pathologie und Funktionen der Regulationen.* Leiden 1936. — Litzner, St.: *Ref. nach Lichtwitz.* — Lommel, F.: *Dtsch. Arch. klin. Med.* 1908: 92: 83. — Lucas, W. S.: *Arch. int. Med.* 1912: 10: 597. — March, H. E.: *Ref. nach Harrop und Wintrobe.* — Mc Alpin, K. R.: *J. am. med. Assoc.* 1929: 92: 1825. — Michels, Nicholas, A.: *Handbook of Hematology* 1938: 1: 231. — Minot, G. R. und Buckman, T. E.: *Am. J. med. Sci.* 1923: 166: 469. — Model, M. und Wolff, A.: *Ref. nach Lichtwitz.* — Morawitz, P.: *Ref. nach Harrop und Wintrobe.* — Morris, R. S.: *J. am. med. Assoc.* 1933: 101: 200. — Mosse, M.: *Z. klin. Med.* 1914: 79: 431. — Naegeli, O.: *Ref. nach Harrop und Wintrobe.* — Oertling, H. und Griggs, J. F.: *J. am. med. Assoc.* 1935: 104: 250. — Oppenheimer, B. S.: *Ref. nach Harrop und Wintrobe.* — Osler, W.: *Am. Journ. Med. Sc.* 1903: 126: 187. — Derselbe: *Brit. Med. Journ.* 1904: 1: 121. — Paschkis, K. und Diamant, M.: *Dtsch. Arch. klin. Med.* 1930: 169: 180. — Reissmann, C.: *Ref. nach Lucas.* — Rennen, K.: *Beitr. Klin. Tbk.* 1922: 53: 197. — Reznikoff, P., Foot, N. C. und Bethca, J. M.: *Am. J. med. Sci.* 1935: 189: 753. — Ringoen, A. R.: *Handbook of Hematology* 1938: 1: 179. — Rist, E.: *Ref. nach Harrop und Wintrobe.* — Rosenthal, Nathan: *Handbook of Hematology* 1938: 1: 447. — Rosin, H.: *Ref. nach Harrop und Wintrobe.* — Röver, F.: *Münch. med. Wschr.* 1911: 58: 2791. — Ryle, J. A.: *Ref. nach Harrop und Wintrobe.* — Sandesky: *Ref. nach Harrop und Wintrobe.* — Schulhoff, K. und Matthies, M. M.: *J. am. med. Assoc.* 1927: 89: 2093. — Seuderling, Y.: *Duodecim* 1937: 53: 815. — Seufert, E. G.: *Am. J. med. Sci.* 1910: 140: 827. — Stransky, E. und Wittenberg, A.: *Ref. nach Harrop und Wintrobe.* — Todtenhaupt, W.: *Dtsch. Arch. klin. Med.* 1927: 154: 79. — Tuchfeld, F.: *Med. Klin.* 1931: 27: 130. — Türk, W.: *Wien. klin. Wschr.* 1904: 17: 153. — Vaquez, H.: *C. r. Soc. Biol.* 1892: 4: 384. — Weber, F. B.: *Brit. med. J.* 1927: 2: 98. — Wieland, W.: *Z. Kinderhk.* 1924: 38: 647. — Derselbe: *Z. Kinderhk.* 1932: 53: 703. — Wilbur, D. L. und Ochsner, H. C.: *Ref. nach Harrop und Wintrobe.* — v. Winterfeld, H. K.: *Z. klin. Med.* 1923: 100: 498. — Winternitz, M. C.: *Arch. int. Med.* 1912: 9: 680. — Zadek, I.: *Ref. nach Harrop und Wintrobe.* — Zimmermann, O.: *Klin. Wschr.* 1934: 13: 696.

# Volumes supplémentaires des Acta Medica Scandinavica publiés 1921—1945.

- I. *Aksel O. Haneborg*: The effects of alcohol upon digestion in the stomach. — 1921.
- II. *Olle P:son Reuterwall*: Über die Elasticität der Gefässwände und die Methoden ihrer näheren Prüfung. — 1921.
- III. Verhandlungen des X. Nordischen Kongresses für innere Medizin zu Helsingfors 30. Juni—2. Juli 1921. — 1922.
- IV. *Karen Marie Hansen*: Investigations on the blood sugar in man. Conditions of oscillations, rise and distribution. — 1923.
- V. *Leonard Brahme*: Arsen in Blut und Cerebrospinalflüssigkeit. — 1923.
- VI. *Harald A. Salvesen*: Studies on the physiology of the parathyroids. — 1923.
- VII. Rapports et comptes rendus du onzième congrès de médecine des Pays du Nord tenu à Kristiania du 3 au 5 juillet 1923. — 1924.
- VIII. *Rolf Hallehol*: Blood sugar studies, with special regard to the threshold of glycosuria in diabetes mellitus and benign chronic glycosuria. — 1924.
- IX. *Sixten Hesser*: Serological studies of human red corpuscles. — 1924.
- X. *Johannes Helweg*: Sciatica or myopathia e labore of the posterior region of the leg. — 1925.
- XI. *Ernst B. Salén*: Studien über die Kältelhämoglobinurie. — 1925.
- XII. *Gösta Ekehorn*: Syphilis fetuum, a critical study of the syphilitic endometritis of the secundines, and of the presence, nature, functions and development of the antibody-producing tissues of the fetal organism. — 1925.
- XIII. *Hans Davide*: Action of anti fibrinogen serum on red corpuscles. — 1925.
- XIV. *Johannes Wahlberg*: Das Thyreotoxikosesyndrom und seine Reaktion bei kleinen Joddosen. — 1926.
- XV. *Adolf F. Lindblom*: Über die Funktionstähigkeit der mit Pneumothorax artificialis behandelten Lunge nach ihrer Wiederentfaltung. — 1926.
- XVI. Rapports et comptes rendus du douzième congrès de médecine des Pays du Nord tenu à Stockholm du 27 au 29 août 1925. — 1926.
- XVII. *Fredrik Leegaard*: Researches regarding the haemodynamics in rabbits in normal condition and during experimental pneumonia. — 1926.
- XVIII. *Martin Odén*: Studien über die Säureproduktion bei Diabetes mellitus. — 1927.
- XIX. *Eskil Kylin*: Der Gehalt des Blutes an Calcium und Kalium. — 1927.
- XX. *Nanna Svartz*: Etude sur les bactéries intestinales iodophiles et spécialement sur les clostridies iodophiles. — 1927.
- XXI. *Eggerl Möller*: Clinical investigations into the basal metabolism in diseases of the thyroid gland. — 1927.

- XXII. *Gustaf A. Lindström*: An experimental study of myelotoxic sera. Therapeutic attempts in myeloid leukaemia. — 1927.
- XXIII. *Ulrik Quensel*: Zytologische Untersuchungen von Ergüssen der Brust- und Bauchhöhlen mit besonderer Berücksichtigung der karzinomatösen Exsudate II. — 1928.
- XXIV. *Ollo Jervell*: Investigation of the concentration of lactic acid in blood and urine. — 1928.
- XXV. *Albert Grönberg*: Beitrag zur Kenntnis der klinischen Verwertbarkeit des Holmgrenschen Frontalreflexes. — 1928.
- XXVI. *Rapports et comptes rendus du treizième congrès de médecine des Pays du Nord tenu à Copenhague du 30 juin au 1 juillet 1927.* — 1928.
- XXVII. *Haquin Malmros*: A study of glucosuria with special reference to the interpretation of the incidental finding of a positive reduction test. — 1928.
- XXVIII. *Claes Grill*: Kavernenstudien. Physikalisch-diagnostische Gesichtspunkte betreffend die Symptomatologie der kavernösen Lungentuberkulose. — 1929.
- XXIX. *Olaf Bang*: Klinische Urobilinstudien. — 1929.
- XXX. *Folke Lindstedt*: Über die Natur der muskelerheumatischen (Myalgischen) Schmerzsymptome. — 1929.
- XXXI. *Gustav Nylin*: Periodical variations in growth, standard metabolism and oxygen capacity of the blood in children. — 1929.
- XXXII. *Johs. Mygge*: Etude sur l'écllosion épidémique de l'influenza. — 1930.
- XXXIII. *Anders Kristenson*: Zur Kenntnis der lokalisierten Thrombenbildungen in der Vena iliaca communis sinistra. — 1930.
- XXXIV. *Verhandlungen des 14. Nord. Kongresses f. innere Medizin zu Helsingfors 28.—30. Juni 1929.* — 1930.
- XXXV. *Alexander Jarolzky*: Zur diätetischen Behandlung des runden Geschwürs des Magens und des Duodenums. — 1930.
- XXXVI. *Gösla Ekehorn*: On the principles of renal function. — 1931.
- XXXVII. *Oline Christensen*: Pathophysiology of hunger pains. — 1931.
- XXXVIII. *Erik Lundberg u. Stina Thyseius-Lundberg*: Beitrag zur Kenntnis des innersekretorischen Gleichgewichtsmechanismus. — 1931.
- XXXIX. *Olaf Romeke*: Der Blutzucker im älteren Alter, insbesondere bei hypertensischen Zuständen. — 1931.
- XL. *Birger Strandell*: Pernicious anemia. A study of 117 cases. — 1931.
- XLI. *Helge Lublin*: On the late symptoms after gastroenterostomy and resection of the stomach (Billroth II) for gastric and duodenal ulcer. — 1931.
- XLII. *Ejnar Jarlov*: The clinical types of abnormal obesity. — 1932.
- XLIII. *Hans Kjærgaard*: Spontaneous pneumothorax in the apparently healthy. — 1932.
- XLIV. *E. Melkersson*: Etudes cliniques sur la réaction myodystonique. — 1932.
- XLV. *Birger Enocksson*: A study of the reducing power of the blood with special reference to some gastro-intestinal diseases and their diagnosis. — 1932.
- XLVI. *Snorre Wohlfahrt*: Die vordere Zentralwindung bei Pyramidenbahnläsionen verschiedener Art. — 1932.
- XLVII. *Helge Nyman*: Studien über Fälle, die mit Achylie resp. Hypochylie assoziiert sind. — 1932.
- XLVIII. *Stig Lindgren*: Eine Studie über depressive Sekretionsanomalien des Magens. — 1932.
- XLIX. *A. Lichtenstein*: Agranulozytose. — 1932.
- L. *Proceedings of the fifteenth Scandinavian congress for internal medicine held in Oslo from 29th June to 1st July 1931.* — 1932.
- LI. *Berzel von Bonsdorff*: Sur Methodik der Blutdruckmessung. — 1932.

- CVI. *Knut Liedholm*: Studien über das Verhalten des Venendruckes beim valsalvaschen Versuch. — 1939.
- CVII. *Jean Lequime*: Le débit cardiaque. — 1940.
- CVIII. Verhandlungen der zweiten Konferenz der internationalen Gesellschaft für biologische Rhythmusforschung am 25. und 26. August 1939, Utrecht (Holland). — 1940.
- CIX. *Per Hedenius*: Über wahre Metachromasie der weissen Blutkörperchen. — 1940.
- CX. *Hans Dijs*: Beiträge zur Diagnostik der Vitamin-C-Mangelkrankheit. — 1940.
- CXI. *Turo Niemi*: Die Senkungsreaktion der roten Blutkörperchen bei Embolien, Thrombosen und Gehirnblutungen sowie einigen anderen Gefässerkrankungen. — 1940.
- CXII. *Hall Scharlum-Hansen*: Das Sternalmark bei leukämischen Krankheiten und die Genese der Monozyten. — 1940.
- CXIII. *Acta medica scandinavica*, author and subject index to vol. 52—100, and supplements 1—100, 1919—1939. — 1940.
- CXIV. *Hugo Jelke*: Über Hyperparathyreoidismus. — 1940.
- CXV. *Håkon Rasmusen*: Influence of the thyroid hormone on heart and circulation. — 1941.
- CXVI. *Jorgen H. Vogt*: The influence of some diet factors on the irritability of the skin and on the mineral contents of the skin and blood plasma in rabbits. — 1941.
- CXVII. *Fredrik Sundelin*: Die Goldbehandlung der chronischen Arthritis unter besonderer Berücksichtigung der Komplikationen. — 1941.
- CXVIII. *John Reenstierna*: Further therapeutic tests with an antileprosy serum. — 1941.
- CXIX. *Olof Nordenfält*: Über funktionelle Veränderungen der P- und T-Zacken im Elektrokardiogramm. — 1941.
- CXX. *Leo Noro*: Untersuchungen über die Trotyl-, Tetryl- und Knallquecksilbervergiftungen bei den Arbeitern der Munitionsfabriken Finnlands. — 1941.
- CXXI. *Aage Lachmann*: Hypoparathyroidism in Denmark. A clinical study. — 1941.
- CXXII. *Carl August Hernberg*: Die Grösse und Form der roten Blutkörperchen bei Menschen verschiedenen Alters unter physiologischen Verhältnissen. — 1941.
- CXXIII. *Rapports et comptes rendus du dix-neuvième congrès de médecine des pays du Nord tenu à Oslo du 27 au 29 Juin 1939.* — 1941.
- CXXIV. *Gösta Widström*: The problem of vaccination against tuberculosis. An experimental study. — 1941.
- CXXV. *Mikael Skjelderup Kobro*: Asthmatic bronchitis. A clinical, pathogenetic and therapeutic study. — 1942.
- CXXVI. *Ole K. Evensen*: Alimentary hypoglycemia after stomach operations and influence of gastric emptying on glucose tolerance curve. — 1942.
- CXXVII. *Karl Östner*: Studien über die Heparinblutsenkungsreaktion und Heparin-Citrat-Blutsenkungsreaktion. — 1942.
- CXXVIII. *Henrik O. Lagerlöf*: Pancreatic function and pancreatic disease studied by means of secretin. — 1942.
- CXXIX. *Torsten Bruce*: Die Silikose als Berufskrankheit in Schweden. Eine klinische und gewerbemedizinische Studie. — 1942.
- CXXX. *Sixten Kallner*: The cyanosis developing during treatment with sulfanilamide preparations. — 1942.
- CXXXI. *Arne Barfred*: Investigations into the biological effects of liver extracts with special reference to the gastric-stimulating principle. — 1942.

- CXXXII. *Carl-Olof Oldfelt*: Oxygen consumption and growth and the effect of immune and normal sera. In vitro studies on two bacterial strains. — 1942.
- CXXXIII. *Per Wisling*: A study of infectious mononucleosis (Pfeiffer's disease) from the etiological point of view. — 1942.
- CXXXIV. *Jorgen E. Thygesen*: The mechanism of blood sedimentation. — 1942.
- CXXXV. *Erik Hedvall*: Bovine tuberculosis in man. A clinical study of bovine tuberculosis, especially pulmonary tuberculosis, in the southernmost part of Sweden, and *Hilding Magnusson*: The relation between bovine and human tuberculosis from the veterinary point of view. — 1942.
- CXXXVI. *Paavo Maijala*: Klinische Untersuchungen über die Häufigkeit und Art der seropositiven Spätlues in Finnland. — 1942.
- CXXXVII. *Thor Sällström*: Das Vorkommen und die Verbreitung der multiplen Sklerose in Schweden. — 1942.
- CXXXVIII. *Fritz Karlström*: The Cl-ion content of the cerebrospinal fluid and its relation to the Cl-ion content of the blood. — 1942.
- CXXXIX. *Bertil Dahlberg*: The masticatory effect. A new test and an analysis of mastication in more or less defective set of teeth. — 1943.
- CXL. *Rolf Hallgren*: Epidemic hepatitis in the county of Västerbotten in northern Sweden. An epidemiological, clinical and etiological study. — 1943.
- CXLI. *Gunnar Löfström*: Nonspecific capsular swelling in pneumococci. A serologic and clinical study. — 1943.
- CXLII. *A. Rune Frisk*: Sulfanilamide derivatives. Chemotherapeutic evaluation of N<sup>1</sup>-substituted sulfanilamides. — 1943.
- CXLIII. *Sven Gard*: Purification of poliomyelitis viruses. Experiments on murine and human strains. — 1943.
- CXLIV. *Einar Hollström*: An investigation into a yeast-like fungus isolated from patients suffering from, or suspected of, pulmonary tuberculosis. — 1943.
- CXLV. *S. Perséus*: The influence of heart glucosides, theophylline and analeptics on the cardiac output in congestive heart failure. With remarks on the acetylene methods for the determination of the arteriovenous oxygen difference. — 1943.
- CXLVI. *Mikko Virkkunen*: Untersuchungen über den Einfluss der Tonsillitis und der Tonsillektomie auf das Sternalpunkttat und das Blutbild. — 1943.
- CXLVII. *Jakob Möllerström*: Das Diabetesproblem. Die rhythmischen Stoffwechselvorgänge. — 1943.
- CXLVIII. *Gunnar Dahlberg*: Mathematische Erblichkeitsanalyse von Populationen. — 1943.
- CXLIX. *Rolf Luft*: A study on hirsutism, Cushing's syndrome and precocious puberty. — 1944.
- CL. *Erik Sköld*: On hemophilia in Sweden and its treatment by blood transfusion. — 1944.
- CLI. *Uno Carlborg*: Studies of circulatory disturbances, pulse wave velocity and pressure pulses in larger arteries in cases of pseudo-xanthoma elasticum and angiod streaks. A contribution to the knowledge of the function of the elastic tissue and the smooth muscles in larger arteries. — 1944.
- CLII. *Richard F. Öhnell*: Pre-excitation. A cardiac abnormality. Pathophysiological, patho-anatomical and clinical studies of an excitatory spread phenomenon bearing upon the problem of the WPW (Wolff, Parkinson and White) electrocardiogram and paroxysmal tachycardia. — 1944.



- CLIII. C. E. *Nylund*: Über die Untersuchungstechnik bei der Bestimmung von Nachtblindheit als Symptom von Vitamin-A-Mangel und Untersuchungen über das Vorkommen von Nachtblindheit und über ihre Abhängigkeit von der Vitamin-A-Zufuhr. — 1944.
- CLIV. Gösta *Birath*: Lung volume and ventilation efficiency. Changes in collapse-treated and non-collapse-treated pulmonary tuberculosis and in pulmonectomy and lobectomy. — 1945.
- CLV. E. V. *Helander*: Über die Magensekretion bei Botlriocephalus-trägern. — 1945.
-

## Ouvrages envoyés aux *Acta medica Scandinavica*.

*Guido Fanconi, Hans Zellweger und Anna Botsztejn*: Die Poliomyelitis und ihre Grenzgebiete. 694 S. 175 Abb. 172 Tab. Preis: geb. schw. Fr. 56. —. Benno Schwabe & Co, Verlag, Basel, Schweiz, 1944.

*Arbejder fra Rigshospitalets Afdeling B*, udgivet af Erik Warburg. 2. ser. vol. IV. 1941—1943. Ejnar Munksgaard, København 1944.

---